Changes in recommendations related to nutrition in pregnancy

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Kumulative Habilitationsschrift zur Erlangung der Venia Legendi

der Universität Zürich für das Fachgebiet

Geburtshilfe, spezielle Klinische Epidemiologie

vorgelegt von

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Zürich 2018

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1. Summary

Factors related to lifestyle influence the course of pregnancy and should, therefore, receive attention during pregnancy counselling. Diet, as the most culture-dependent factor was, and still is, subject of debate among experts. Women, especially pregnant women, frequently seek advice on diet and nutrients from their gynaecologist.

The following report summarizes some of the current discussions about diet recommendations at both the macronutrient and the micronutrient level. Based on the recommendations for weight changes during pregnancy, macronutrient intake, supplementation of folic acid, iron, vitamin D, and iodine, this report explains the challenges of nutrition counselling in daily practice.

In conclusion, dietary reference intakes for almost all nutrients are extrapolated from data on the non-pregnant body. The data on basic metabolic needs for the changing pregnant body are mostly missing or have been measured many years ago with today inappropriate analyses.

Therefore, further research is needed to determine these metabolic changes. The knowledge of a general healthy diet during pregnancy should be promoted during counselling, ideally by nutritionists.

2. Abbreviations

ACOG	American Congress of Obstetricians and Gynaecologists
BMI	Body mass index
DACH	Consortium for reference values in diet in Germany, Austria and Switzerland
EEK	Eidgenössische Ernährungskommission
IOM	Institute of Medicine
NICE	National Institute for Health and Care Excellence
OR	Odds ratio (aOR adjusted odds ratio)
SGE	Schweizerische Gesellschaft für Ernährung

3. Changes in recommendations

The wellbeing of pregnant women, and consecutively their children, gets high priority in many societies. For wellbeing and health, an adequate diet is of great importance. Pregnant women are seeking for information about diet and nutrition in this special phase and find it from various sources: their mothers, friends, books, and, most frequently, the internet. They often find conflicting information, leading to insecurity and misunderstanding. Often, pregnant women come with their gathered information to their gynaecologist and ask about clarification and further information. In order to be able to council pregnant women, a gynaecologist needs to keep abreast of the most recent research results on a healthy diet and the use of supplementation. Over the last 50 years the recommendations for weight gain and specific nutrients have varied to a large extent [1]. Over the last 20 years, the focus has shifted more to the micronutrients because new laboratory analyses have been widely available. Nevertheless, the increase in overweight and obesity rates among women of reproductive age has forced the medical community to focus on energy intake as well.

Hyperemesis and tiredness reduce the wellbeing of many women in the first trimester of pregnancy. The energy intake does not have to be increased in this period, even though some women feel a relief in the hyperemesis if they eat, which can result in an undesired weight gain already early on in pregnancy. From the second trimester onwards, the body changes become more visible and there is a demand for more energy. Besides the changes in the amount of macronutrients and their relative distribution, there seems also to be a greater need for many micronutrients. Folic acid, iron, vitamin D, calcium, iodine, and zinc [2] are needed for the growth of the fetus, the placenta and the additional maternal tissues. Whereas the importance of pre-conceptional intake of folic acid for the reduction of neural tube defects is well known, the importance of pre-conception levels of other nutrients and their influence in the course of pregnancy have been less extensively examined.

The recommendations for the intake of macronutrients and micronutrients have undergone, and are still undergoing, several revisions. Some of the macronutrients and micronutrients are showing clear benefits for both mother and child, others are

providing more confusing data, leaving it up to the gynaecologist to judge the necessity of supplementation.
Research over the past years has led to changes in perspective what pregnant women should eat and what should be supplemented and, as current research shows, the recommendations need to be adapted in the future.
Nevertheless, pregnancy is an ideal window of opportunity to improve the diet and health of both mother and child in the future [3].

The aim of this paper is first to discuss the status of research and second to enlighten the changes in the recommendations for pregnant women concerning weight gain and certain nutrient intake in pregnancy.

3.1 Weight loss and weight gain in pregnancy
Weight gain in pregnancy is a physiological process. Thus, voluntary weight loss is not recommended. Weight loss and limited weight gain are related to small-for-gestational-age infants at birth [4]. Grooten et al. even found increased blood pressure among the children (five to six years old) of women with severe weight loss (> 5kg) in early pregnancy [5]. Weight loss due to severe hyperemesis in the first trimester is found in 0.3 - 2% of pregnancies [6]. Hyperemesis seems to be associated with an increase in the level of human chorionic gonadotropin in the blood [7]. The immediate consequences of weight loss include mainly dehydration and electrolyte imbalance [8, 9]. Stationary treatment is usually necessary and includes hydration, as well as doses of doxylamine and pyridoxine [6]. Additional interventions include treatment with ondansetron or dopamine antagonists, such as metoclopramide or promethazine. A novelty in this field of research is the discovery of possible causal relationship between *Helicobacter pylori* infection and hyperemesis in these women. In a study done in the Netherlands, *H. pylori*-positive women were more likely to report daily vomiting than women without *H. pylori* infection (aOR, 1.44; 95% CI 1.16 - 1.78) [10].

Excessive weight gain in the first half of pregnancy has been correlated to an increased risk of elevated body fat in the newborn, even when compared to women with overall excessive weight gain during pregnancy (OR 2.64, 95% CI 1.35 - 5.17) [11]. This effect lasted until mid-childhood, when a higher rate of gestational weight

gain in the first trimester is also associated with a greater risk of obesity (OR 1.31; 95% CI 1.10 - 1.55) [12]. The obstetrical consequences of a weight gain higher than recommended have been documented in several studies [13]. Besides the consequences for the child who is at risk of macrosomia, preterm delivery, or, surprisingly, small-for-gestational-age, severe weight gain in pregnancy bears considerable risks for the mother as well. As Linne et al. showed in a 15-year follow-up, excessive weight gain leads to an increased risk for the mother to be overweight or obese later in life [14].

Weight gain recommendations have been extensively discussed for 100 years. Until the 1960s, excessive weight gain was related to, and even seen as the cause for preeclampsia. But the trend turned when small-for-gestational weight babies seemed to be related to restricted weight gain. The most important factor for gestational weight gain seems to be the pre-pregnancy weight or body mass index (BM)I: The higher the pre-pregnancy BMI is, the higher is the risk of excessive weight gain. In a Swiss cohort, we could demonstrate that the prevalence of increased BMI (> 25) is between 8% and 50%, depending on the cultural background of the pregnant woman [15]. Increased weight gain already in the first three months should be avoided or limited to 2 kg [16]. Nevertheless, about 10 - 20% of all pregnant women gain more than 2kg in the first months [17]. The weight gain recommendations during pregnancy in many western countries refer to the IOM guidelines issued in 2009 [18]. These guidelines are based on maternal BMI before pregnancy and give a trajectory on how much weight a pregnant woman should gain during pregnancy [16]. The recommendations also state the additional weight that should be gained per week, beginning in the second trimester, for each pre-pregnancy BMI group. Studies in Switzerland showed that about 40 - 45% of pregnant women gain more than recommended [15, 19, 20]. The recommendations of the European consortium for nutrient intake, DACH, supports no additional calories in the first trimester for pregnant women, 250 kcal/day more than the calories needed for a non-pregnant women in the second trimester and 500 kcal/day more in the third trimester [2]. The number of calories needed depends on the age and physical activity and ranges from 1’800 kcal/day for sedentary behaviour (e.g. office job) to 2’400 kcal/day for physically active behaviour (e.g. shop assistant). Therefore, only an analysis of the daily activity can reveal the appropriate intake of calories per day.

3.2 Macronutrients

The need for all three macronutrients, fat, protein as well as carbohydrates, increases during the pregnancy, with the highest increase in protein. The fetus and placenta are built as extra tissues, but maternal tissues changes as well. The maternal fat stores increase by around 3.5kg, mainly in preparation of breastfeeding [21]. If the recommended macronutrient intake is either exceeded or not reached, there can be negative consequences for both the fetus and the mother. Blumfield et al. showed in a review, that the energy and macronutrient intakes of pregnant women do not match national recommendations in developed countries [22]. We investigated the total fat intake and found a higher risk for vaginal infection with *Gardnerella vaginalis* (adjusted OR = 3.6, 95% CI = 1.3 - 10, p = 0.01) for the women who consumed higher-than-recommended amounts of fat compared to those with a normal fat intake [23]. These results warrant further investigation, but also point at the need for a careful choice of food when it comes to fatty acids and total fat intake. Godfrey et al. studied 538 pregnant women and found that a high carbohydrate intake in early pregnancy suppresses placental growth, especially if combined with a low dairy protein intake in late pregnancy [24].

According to the current knowledge, the macronutrients in diet should be split as follows: 45 - 55% in carbohydrates (200 - 250g/d), 30 - 35% fat (80 - 95g/d) and 10 - 15% protein (50 - 60g/d) [2, 22]. Too little protein intake can lead to low birth weight and preterm delivery among undernourished women [25]. The intake of polyunsaturated fatty acids is of specific importance. Inadequate omega-3-fatty acids intake has been related to changes in birth weight and increased risk for preterm delivery [26, 27]. Additionally, there is a positive association between the visual and neurological development of infants and the adequate intake of omega-3-fatty acids of their mothers in pregnancy [28].

3.3 Micronutrients

The growing fetus needs a greater amount of various micronutrients in the course of pregnancy. In the pre-conception phase, folic acid intake should be increased to reduce the risk of a neural tube defect. Recent research suggests that 5-methyl-tetrahydrofolate can be an alternative supplement to folic acid supplementation. Due to genetic polymorphisms, some women cannot metabolize folic acid to dihydrofolate and tetrahydrofolate [29], which are the biologically active forms of folic acid. The

supplementation with 5-methyl-tetrahydrofolate would also allow the timely detection of vitamin B12 deficiency, as vitamin B12 is required for folate metabolism [30]. Due to the costs involved and ethical questions, 5-methyl-hyrdotetrafolate has not been tested in a randomized controlled trial. Nevertheless, the biological variability calls for further investigation in pregnant women and women who plan to get pregnant.
If folic acid is taken correctly, either as a supplement or as fortification in flour, the risk of neural tube defects can be reduced by up to 75% [31, 32]. The most recent analysis of folic acid intake in the U.S. has concluded that despite fortification of flour, about a quarter of the population has only suboptimal red blood cell folate concentrations due to variations in intake [33]. The authors concluded that folic acid supplement use is still important. As for other inborn abnormalities, the Cochrane report in 2015 did not find any benefits of folic acid supplementation [34].

Iron is necessary during pregnancy to increase the blood production of the mother as well as to produce blood in the fetus. Currently the investigated question whether the absorption of iron in the gut is related to the BMI of the mother at the beginning of pregnancy. Due to the relation between obesity and increased inflammatory reactions in the gut and blood, it is unclear if women with normal body weight absorb iron in the same amounts as obese women do. First results show a dramatically reduced increase in fractional iron absorption in overweight/obese pregnant women [35]. The authors speculate that hepcidin may modulates iron absorption even in the third trimester. Thus, even though iron demands are strongly increased, obesity may prohibit adequate iron supply to the expecting mother and the fetus due to persistent subclinical inflammation.
The relationship between iron deficiency and gestational diabetes has gained interest in recent years [36]. Iron is a transition metal and has a potential pro-oxidant role, whereas gestational diabetes is associated with elevated levels of oxidative stress [37]. Two randomized trials in Finland (Kinnunen 2014: n=2944) and in Hong-Kong (Chan 2009: n=1’164) on the intake of iron supplementation in early pregnancy found greater risk of glucose intolerance [38, 39]. A limitation of the Finnish study was that it did not measure the iron status biomarkers. Therefore, it is still unclear whether the iron status modifies the influence of supplemented iron on the risk of developing a glucose-intolerance-related outcome. Further studies are needed to determine risk groups in iron supplementation [40, 41].

Nevertheless, a huge body of literature indicates the benefits of iron supplementation during pregnancy. According to the guidelines of the SGGG, haemoglobin and ferritin should be tested in all pregnant women at the beginning of pregnancy to determine the iron status and, thereafter, followed by appropriate iron supplementation orally or intravenously [42]. The combination of folic acid and iron show an improvement in the lower rate of preterm births and small-for-gestational-age children in low- and middle income countries, where micronutrient deficiencies are common [43].

Vitamin D is involved in calcium homoeostasis through regulation of calcium up-take in the gut and is a part in several immune-regulatory processes. Cholecalciferol (vitamin D3) is synthesized in the skin by sunlight (UVB) from 7-dehydrocholesterol. This is followed by its transformation to the active form 25-hydroxyvitamin D [25(OH)D] in the liver. Vitamin D sources in food are scarce and especially in winter supplementation is recommended. The prevalence of vitamin D deficiency in Switzerland in pregnant women ranges from 50% to 60% and is dependent on the trimester and skin type of the mother [44, 45]. The importance of vitamin D during pregnancy has gained a lot of interest in recent years. This happened mainly after the recommended supplementation for the general population and for pregnant women rose from 5µg to 15µg vitamin D daily in 2009, and recently to 20 µg per day [2, 46, 47]. These changes were introduced as the associations between vitamin D and bone health as well as the risk for various chronic diseases became evident. Epidemiological studies have shown that a low vitamin D status is associated with an increased risk of gestational diabetes [48, 49], preeclampsia [50, 51], caesarean section [52, 53], preterm delivery [54] and, in some ethnicities for low birth weight [55]. Several guidelines include recommendations for vitamin D supplementations in pregnancy (NICE, ACOG, EEK) at 15 - 20µg per day. Several randomized controlled trials have been performed on the effect of vitamin D supplementation on pregnancy complications. Wagner et al. found a reduced risk for overall comorbidities (OR 0.84 95%CI 0.74 - 0.95) during pregnancy for women with 25(OH) vitamin D levels above 32µg/ml [56]. For preeclampsia, a Cochrane Review concluded that there is a trend of risk reduction with vitamin D supplementation (RR 0.52 95% CI 0.25 - 1.05) [57]. But in combination with calcium and vitamin D, it reduced the risk significantly (RR 0.51 95%CI 0.32 - 0.8). The prevention of gestational diabetes by vitamin D

supplementations has also been investigated, and several reviews have concluded that vitamin D has no potential to prevent diabetes [57, 58]. The intervention trials for gestational diabetes have used different dosages and times of application, showing trends of risk reduction for gestational diabetes when used in high dosages. Zhou et al. showed in a meta-analysis of six trials, 1'687 women included, that supplementation with vitamin D can reduce the risk of preterm delivery (OR 0.57 95%CI 0.36 - 0.91) [59]. The amount of supplementation varied, however, in all six trials.

Iodine is particularly important in pregnancy for the brain development and growth of the fetus. Iodine is the main constituent of the thyroid hormones. Disturbances of iodine metabolism lead to large impairment of the fetus. For iodine intake, 250µg iodine/day is recommended for pregnant women, resulting in a urinary iodine concentration of 150µg/l [60]. This urinary iodine concentration of 150µg was considered necessary to guarantee low rates of cognitive impairment of the children later in life. Iodine coverage in Switzerland has been traditionally good due to the fortification in table salt. It is recommended that at the population level, the median urinary iodine concentration (UIC) should reach 150µg/L. In 2014, the amount of fortification was increased due to decreasing levels of UIC in pregnant women in the previous national surveys - from 249µg/L in 2004 to 162µg/L in 2009 [61, 62]. Opposite to what was expected, the survey in 2015 showed an even lower UIC among pregnant women, falling from 162µg/L to 140µg/ml [63].
Additionally, a recent study focusing on iodine supplementation in two mildly deficient populations of pregnant women has not shown any improvement in the cognitive outcome in five-year-old children compared to women who received no iodine supplementation [64]. These results challenge the question of whether a median UIC of 150µg/L, and, therefore, the supplementation with 250µg/day, is necessary for the wellbeing of the mothers and her offspring. In Switzerland, the use of iodized household salt should be recommended in pregnancy. This recurrent low UIC led to the discussion on prescribing multivitamin tablets, which include 150µg iodine, to pregnant women. A special tablet containing just 150µg iodine is currently not available in Switzerland.

3.4 Conclusions

In conclusion, the counselling of pregnant women in such important fields like weight gain and diet, including supplement intake, has not yet reached a final conclusion. Weight gain is necessary in pregnancy, but its extent should be carefully discussed with the pregnant woman as early as possible. Preferably, the topic should arise before the woman gets pregnant since the BMI before pregnancy has the most important influence on the pregnancy outcome for both mother and child. Advertisements or other interventions intended to reach broad population might help to sensitize future mothers. Discussing weight gain only in the third trimester, when all recommendations come too late, is not helpful. Rather, it is stressful for the pregnant woman. The IOM weight gain recommendations give a guideline for women. If known early enough, they can also be followed. The German guidelines suggest a weight gain of 10 to 16kg for normal-weight women [65]. Overweight and obese women should be informed about the long-lasting effects of increased weight gain such as weight retention and obesity in the future.

The first pregnancy counselling should include a discussion on weight gain as well as an appropriate diet. Due to hyperemesis gravidarum, the discussion on diet should be repeated at a later stage in pregnancy to follow up on the recommendations. Hyperemesis can influence weight gain and whereas moderate weight loss can be compensated later in pregnancy, inappropriate weight gain is more difficult to compensate during pregnancy. A well-balanced diet according to the food pyramid [66], which will add 250kcal in the second and 500kcal in the third trimester, should be recommended to all pregnant women.

The obstetricians and general practitioners should motivate pregnant women to adhere to the recommendations about macronutrients in their diet or at least be able to inform pregnant women about the recommendations. As mentioned before, certain combinations can have especially strong consequences for both mother and child.

In the field of micronutrients, only the studies on folic acid have provided unrestricted evidence that its supplementation improves the health of the fetus. For all the other micronutrients, there is mostly a trend of improvement, which has been frequently

demonstrated in epidemiological studies. But the evidence of clinical importance for either the mother or the child or both is missing in most cases. Due to ethical considerations, not all the micronutrients can be tested in randomized controlled trials anymore. But, as in the case of iodine, studies to determine the actual need for iodine in pregnancy or dietary reference intake values for pregnant women are necessary in order to improve the counselling of pregnant women in future.

4. General aims and conclusions of the studies presented

In the daily clinical counselling of pregnant women, it is important to have reliable information at hand. For broadly valid recommendations, first, the population of pregnant women should be characterized. In *Publication I*, for the first time in Switzerland a large group of pregnant women was described in terms of their pre-pregnancy weight as well as weight gain during pregnancy in relation to their ethnic background. The study showed striking differences, which are important for counselling.

Similar is true for *Publication II,* in which the prevalence of vitamin D deficiency in early pregnancy was assessed in women with different skin colours. The overall prevalence of vitamin D deficiency was surprisingly high. This made it clear that vitamin D supplementation should be properly addressed in clinical counselling.

In *Publication III*, vitamin D was measured in the mother and in the umbilical cord as the proxy for the child's vitamin D level around the delivery time. This multicentre study did demonstrated that besides ethnic background, also the geographical location in Switzerland also influences vitamin D levels. Whereas in Bellinzona (sunny part of Switzerland), only 33% of all mothers were vitamin D deficient, 70% of mothers in Samedan (mountain region of Switzerland) had vitamin D deficiency. Therefore, clinical counselling should be adapted to various geographical influences.

5. Presented publications

5.1 Publication I

Quack Loetscher KC, Selvin S, Zimmermann R, Abrams B (2007)

Ethnic-cultural background, maternal body size and pregnancy outcomes in a diverse Swiss cohort.

Women & Health, May 44(4)

Women & Health

ISSN: 0363-0242 (Print) 1541-0331 (Online) Journal homepage: http://www.tandfonline.com/loi/wwah20

Ethnic-Cultural Background, Maternal Body Size and Pregnancy Outcomes in a Diverse Swiss Cohort

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To cite this article: Katharina C. Quack Loetscher MD , Steve Selvin PhD , Roland Zimmermann MD & Barbara Abrams DrPH and RD (2007) Ethnic-Cultural Background, Maternal Body Size and Pregnancy Outcomes in a Diverse Swiss Cohort, Women & Health, 45:2, 25-40, DOI: 10.1300/J013v45n02_02

To link to this article: https://doi.org/10.1300/J013v45n02_02

Published online: 10 Oct 2008.

Ethnic-Cultural Background, Maternal Body Size and Pregnancy Outcomes in a Diverse Swiss Cohort

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ABSTRACT. *Objective*: To investigate the influence of ethnic-cultural background and maternal body size on pregnancy outcomes in infants born at term.

Study design: A retrospective cohort of 1,432 pregnant women who delivered a live newborn at term between 1999 and 2003 provided the data for the following study. We performed multivariable regression analyses for birth weight and rate of caesarean section controlling for

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This research project was funded by the foundation Stiefel-Zangger-Stiftung and the Fond zur Foerderung des Akademischen Nachwuchses of the University Zürich, Switzerland.

The data were collected in the Department of Obstetrics at the University Hospital Zurich, Switzerland, and the data analysis was performed in the Divisions of Epidemiology and Biostatistics at the School of Public Health, University of California, Berkeley, USA.

Women & Health, Vol. 45(2) 2007
Available online at http://wh.haworthpress.com

doi:10.1300/J013v45n02_02

body mass index (BMI), net weight gain, maternal age, parity, smoking, marital status and sex of infant.

Results: Thirty percent of the women studied had a BMI ≥ 25; the proportion of mothers with a BMI ≥ 25 varied substantially by ethnic-cultural background (range: Far East 2.8% vs. Africa 50.0%). After adjustment for confounding variables, mothers from Sri Lanka and the Middle East had significantly lighter infants (Sri Lanka −145.5 g, 95% CI −59.3 g to −231.7 g, $P = 0.001$; Middle East −214.3 g, 95% CI −33.7 g to −395.0 g, $P = 0.02$) than mothers from Switzerland. Each unit increase in maternal pre-pregnancy BMI was associated with a 20.3 g increase in birth weight (95% CI 14.3 g to 26.4 g, $P < 0.001$). Muslim mothers from the former Yugoslavia had significantly lower odds of caesarean section than Swiss mothers (OR 0.63, 95% CI 0.41 to 0.96, $P = 0.03$).

Conclusions: In this cohort, certain ethnic-cultural groups had increased odds for low birth weight and others had reduced odds of operative delivery compared with the Swiss comparison group. Given the strong association between ethnic-cultural background and overweight in this cohort, culturally appropriate support and counseling during prenatal care should be evaluated in the increasingly diverse environment in European countries. doi:10.1300/J013v45n02_02

KEYWORDS. Birth weight, caesarean section, body mass index (BMI), ethnicity, epidemiology

INTRODUCTION

Europe has seen increasing immigration in both numbers and ethnic diversity over the last two decades. Health care providers require more expertise in cultural competence as pregnant women from different ethnic-cultural backgrounds present for prenatal care in greater numbers. Most immigrants have been characterized by a low socioeconomic status and high fertility compared with the host country (Laczko, 2002). These changing demographic factors may influence perinatal outcome. No study in Switzerland has investigated differences in pregnancy outcomes, such as infant birth weight or caesarean section in different ethnic-cultural groups compared with the host population.

However, studies conducted in other European countries have contrasted pregnancy outcomes in the host population with the immigrant population (Diani, Zanconato, Foschi, Turinetto, & Franchi, 2003; Festini, Reali, Taccetti, Repetto, & de Martino, 2004; Guendelman, Buekens, Blondel, Kaminski, Notzon, & Masuy-Stroobant, 1999; Margetts, Mohd Yusof, Al Dallal, & Jackson, 2002; Roville-Sausse, Truc, & Jacob, 2001; Vahratian, Buekens, Delvaux, Boutsen, Wang, & Kupper, 2004; Vangen, Stoltenberg, Skjaerven, Magnus, Harris, & Stray-Pedersen, 2002). Some studies report lower birth weight in infants from different Asian countries compared with the host country (Margetts et al., 2002; Roville-Sausse, Truc, & Jacob, 2001), whereas other studies show similar or higher birth weight, specifically in Chinese infants (Festini et al., 2004; Roville-Sausse, Truc, & Jacob, 2001). Birth weight of infants of immigrant African mothers has been reported as lower, similar or higher than in infants from the host country (Buekens, Masuy-Stroobant, & Delvaux, 1998; Guendelman et al., 1999; Roville-Sausse, Truc, & Jacob, 2001; Vahratian et al., 2004; Vangen et al., 2002). Studies from Scandinavia and the UK also show different nutritional habits and beliefs in immigrant, compared with native, pregnant women (Ahlqvist & Wirfalt, 2000; Eaton, Wharton, & Wharton, 1984; Wharton, Eaton, & Wharton, 1984).

The frequency of caesarean section rates has been reported to be influenced by ethnic-cultural background in various populations, with a higher risk for most immigrant groups compared with the host population (Ibison, 2005; Vangen, Stoltenberg, Skrondal, Magnus, & Stray-Pedersen, 2000). Excess pre-pregnancy weight has been associated with adverse pregnancy outcomes, particularly increased risk of caesarean section (Dietz, Callaghan, Morrow, & Cogswell, 2005).

This study explores the influence of different ethnic-cultural backgrounds and maternal body mass index (BMI) on pregnancy outcomes, specifically birth weight and odds of having a caesarean section, in a cohort of recently immigrated mothers relative to comparable women of Swiss nationality.

MATERIALS AND METHODS

Between January 1999 and December 2003, 8,078 singleton infants were delivered at term (37-42 weeks of gestation) in the Clinic of Obstetrics at the Zürich University Hospital. As this hospital is a tertiary center for obstetrical care with referrals of many high risk patients, to

avoid referral bias we excluded women from this study who were not seen every trimester in our prenatal outpatient clinic (n = 6,406). Including only regularly seen patients, beginning in the first trimester, allowed us to reduce recall bias for pre-pregnancy weight and to ensure equal amounts of prenatal care. We chose only the first pregnancy of mothers who had more than one pregnancy during the study period (n = 231). Nine women with preeclampsia were excluded owing to interference of the disease with birth weight and mode of delivery. After applying these selection criteria, 1,432 pregnancies were available for analysis. Pre-pregnancy weight, age of the mother, parity, smoking status and marital status were self-reported; height was measured in centimeters at the first antenatal visit. Maternal pre-pregnancy body size was characterized by BMI (kg/m^2). Maternal total weight gain at delivery was measured within 1 week before delivery on a digital platform balance in street clothes without shoes. Mode of delivery was recorded at delivery and divided into vaginal delivery (spontaneous, vacuum or forceps) and caesarean section. The gestational age was confirmed by ultrasound in the first trimester, and the birth weight of the infant was measured immediately after delivery. Smoking status was divided into "smoking" or "not smoking" during pregnancy, and marital status was classified as "married" and "other than married." The diagnosis for gestational diabetes was based on a 6 hours fasting glucose screening (Perucchini, Fischer, Spinas, Huch, Huch, & Lehmann, 1999) and confirmed by a 75 g oral glucose test.

The women were categorized according to their ethnic-cultural background, based on geography, religion and self-identified ethnicity (Table 1). Clinical experience suggested that the largest immigrant group, women from the former Yugoslavia, should be further characterized by religion and culture (Muslim vs. non-Muslim). The remaining Caucasian women were grouped by geographical areas of origin into North/East and South Europe owing to small numbers of women from each single country. Turkish and Sri Lankan mothers were kept separate as well because of large numbers. Asian women were split by region into Middle East, South Asia and Far East (Columbia University, 2001). All other women were classified as African or Latin American. All immigrant women were foreign-born, and these groups were compared with women with Swiss nationality, which largely comprised native Swiss women but also included immigrants with Swiss citizenship (which requires a minimum of 5 years residence in Switzerland).

TABLE 1. Distribution of Countries of Origin

Ethnic-Cultural Group	n	Country of Origin
Switzerland	262	
North and East Europe	88	Austria, Belgium, Bulgaria, Czech Rep., Finland, France, Germany, Hungary, Ireland, Netherlands, Poland, Rumania, Russia, Slovakia, Sweden, UK, Ukraine
South Europe	125	Italy, Portugal, Spain
F. Yugoslavia, non-Muslim	112	
F. Yugoslavia, Muslim	308	
Turkey	95	
Sri Lanka	173	
Middle East	24	Iraq, Iran, Israel, Lebanon, Syria
South Asia	36	Afghanistan, Bangladesh, India, Nepal, Pakistan
Far East	36	Cambodia, China, Japan, Korea, Malaysia, Philippines, Thailand
Latin America	51	Brazil, Chile, Columbia, Cuba, Dominica, Dom. Republic, Ecuador, Jamaica, Peru, Venezuela
Africa	112	Algeria, Angola, Cameroon, Congo, Egypt, Eritrea, Ethiopia, Ghana, Ivory Coast, Kenya, Libya, Morocco, Nigeria, Senegal, Somalia, Togo, Tunisia, Zaire

Statistical Analysis

To describe the associations among ethnic-cultural background, pre-pregnancy BMI, and birth weight, a linear multivariable analysis was used, adjusting for net weight gain of the mother (weight at delivery–pre-pregnancy weight–birth weight of the infant (Institute of Medicine, 1990), maternal age, parity, sex of the infant, smoking status and marital status. To identify clearly differences in birth weight associated with pre-pregnancy BMI and maternal ethnic-cultural background, two-way interactions were estimated, using the inclusion criterion of a *P*-value less than 0.1. In an extended model, we included gestational diabetes to evaluate its influence on birth weight as well as its confounding influence on the other variables analyzed.

To describe the association between ethnic-cultural background and delivering by caesarean section, a multivariable logistic analysis was used, including pre-pregnancy BMI, net weight gain of the mother, maternal age, parity, birth weight and smoking status. Gestational diabetes was not included in this analysis because the diagnosis of gestational diabetes itself is not an indication for caesarean section. To confirm this assumption, we included gestational diabetes in an extended model. An assessment of these data suggested that birth weight did not have a linear relationship with mode of delivery; therefore, a quadratic relationship was used to produce a more accurate representation of the relationship between birth weight and mode of delivery. To identify differences in odds of caesarean section associated with maternal ethnic-cultural background, two-way interactions were estimated and evaluated, using the inclusion criterion of a *P*-value less than 0.1. To determine whether the study findings might be biased owing to missing data on history of prior caesarean section, we repeated the analysis limited to primiparous women only.

This study was approved under the ethic and human subjects policy of the University Hospital Zürich which covers all data that are generated in the hospital and anonymously analyzed. The study was exempt from ethical approval by the *Committee for Protection of Human Subjects* at the University of California, Berkeley. No additional written informed consent from study participants was obtained.

RESULTS

The largest group of women came from the former Yugoslavia (29.3%), and women with Swiss nationality comprised about 20% of the study cohort (Table 2). Mean pre-pregnancy weight ranged from 50.9 kg in Far Eastern mothers to 66.4 kg in African mothers. Mean pre-pregnancy BMI in the whole cohort was 23.6 and ranged from 20.3 in Far Eastern mothers to about 25 in African and Turkish mothers. These differences were also reflected in the percentage of mothers who had a BMI ≥ 25 (the former Yugoslavia Muslims 34.4%, Southern Europe 37.6%, Middle East 41.7%, Turkey 42.1%, Africa 50.0%). In the entire cohort 8.4% women smoked during pregnancy, 84.4% of the women were married and 46.9% were delivering their first child. The overall rate of gestational diabetes was 5.8%, and the rate was highest in mothers from Sri Lanka (15%). According to the Institute of Medicine recommendations for total weight gain during pregnancy that are based on maternal

TABLE 2. Characteristics of Women Who Delivered Between 37 and 42 Weeks Gestation at the University Hospital Zürich by Ethnic-Cultural Background (n = 1432)

	n	Age of the Mother (Years)	Pre-Pregnancy Weight (kg)	Height (cm)	Pre-Pregnancy BMI (kg/m^2)	Net Weight Gain (kg)	Gestational Diabetes	BMI > 25	BMI > 30	Birth Weight (g)	Caesarean Section
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	%	%	%	Mean (SD)	%
Switzerland	262	30.6 (6.2)	63.2 (13.8)	166 (7)	22.9 (4.5)	10.9 (6.0)	2.7	22.9	8.0	3376 (448)	33.2
North and East Europe	88	30.9 (5.2)	60.8 (9.1)	167 (6)	21.8 (2.9)	11.8 (5.2)	4.5	6.8	2.3	3468 (463)	31.8
South Europe	125	30.4 (5.1)	64.6 (13.3)	162 (6)	24.6 (4.9)	11.9 (5.8)	7.2	37.6	11.2	3389 (427)	40.8
F. Yugoslavia, non-Muslim	112	26.8 (4.9)	61.8 (10.7)	164 (7)	22.9 (3.8)	13.2 (5.8)	4.5	24.1	3.6	3470 (516)	22.3
F. Yugoslavia, Muslim	308	26.1 (5.4)	63.1 (11.4)	162 (6)	24.1 (4.3)	11.3 (6.4)	4.5	34.4	10.1	3489 (442)	19.2
Turkey	95	27.1 (5.4)	64.1 (12.5)	160 (5)	25.2 (4.9)	11.6 (7.5)	3.2	42.1	16.8	3436 (442)	25.3
Sri Lanka	173	30.2 (4.7)	57.7 (10.3)	157 (7)	23.4 (3.6)	8.4 (5.2)	15.0	34.1	4.6	3264 (422)	40.5
Middle East	24	27.6 (4.8)	61.6 (12.0)	159 (8)	24.2 (4.0)	11.3 (5.3)	4.2	41.7	8.3	3256 (395)	16.7
South Asia	36	27.9 (3.6)	57.4 (8.8)	158 (6)	22.8 (3.1)	10.3 (4.6)	2.8	19.4	2.8	3273 (496)	33.3
Far East	36	30.0 (6.7)	50.9 (7.8)	158 (5)	20.3 (2.7)	11.6 (5.2)	8.3	2.8	0.0	3431 (389)	30.6
Latin America	55	28.6 (6.2)	60.0 (12.0)	160 (8)	23.3 (4.1)	11.5 (6.2)	7.3	23.6	5.5	3341 (398)	32.7
Africa	118	29.2 (5.9)	66.4 (14.5)	162 (7)	25.3 (4.7)	9.0 (7.1)	5.1	50.0	16.1	3413 (469)	31.4
Total	1432	28.7 (5.8)	62.1 (12.3)	162 (7)	23.6 (4.3)	10.9 (6.2)	5.8	30.4	8.5	3404 (452)	29.7

pre-pregnancy BMI (Institute of Medicine, 1990), 39.9% of all women had a total weight gain above the recommended range.

The multivariable linear regression analysis (Table 3) suggested that parity and male sex of the infant were positively associated with birth

TABLE 3. Multivariate Linear Regression Analysis of Factors Related to Birth Weight

	Parameter Estimate	95% CI		*P* Value
Intercept	2718.2	2542.3	2515.6	2920.7
BMI (kg/m^2)	20.3	14.3	26.4	$<$ 0.001
Maternal age (years)	−2.3	−7.2	2.6	0.363
Smoking status				
Non-smoking	Ref.			
Smoking	−173.9	−260.6	−87.2	$<$ 0.001
Parity	49.5	24.0	74.9	$<$ 0.001
Marital status				
Married	Ref.			
Other than married	−42.5	−112.4	27.5	0.234
Net weight gain (kg)	13.7	9.7	17.7	$<$ 0.001
Sex of infant				
Female infant	Ref.			
Male infant	143.1	96.4	189.8	$<$ 0.001
Ethnic-cultural background				
Switzerland	Ref.			
North and East Europe	80.0	−24.3	184.3	0.133
F. Yugoslavia, non-Muslim	35.2	−64.2	134.6	0.488
F. Yugoslavia, Muslim	35.1	−44.8	115.0	0.389
Turkey	−44.8	−150.4	60.8	0.405
Sri Lanka	−145.5	−231.7	−59.3	0.001
Middle East	−214.3	−395.0	−33.7	0.020
South Asia	−150.8	−302.4	0.8	0.051
Far East	36.2	−113.7	186.2	0.636
Latin America	−62.0	−186.1	62.2	0.328
Africa	−67.0	−164.7	30.6	0.178

weight, while smoking was negatively associated ($P \leq 0.001$). No race-ethnicity interaction was observed with these variables, but we found a significant interaction between BMI and Southern European ethnicity (–20.7 g, 95% CI –39.9 g to –1.5 g, $P = 0.034$). Therefore, we excluded Southern European mothers from the final model. In the rest of the cohort, the results indicated a significant increase in birth weight of 20.3 g (95% CI 14.3 g to 26.4 g, $P < 0.001$) per one unit increase in pre-pregnancy BMI, whereas each kilogram of net weight gain during pregnancy increased birth weight by 13.7 g (95% CI 9.7 g to 17.7 g, $P < 0.001$).

Of the different ethnic-cultural backgrounds, Sri Lankan and Middle Eastern ethnicity were significantly related to birth weight, with Sri Lankan infants being on average 145.5 g lighter (95% CI –59.3 g to –231.7 g, $P = 0.001$) and Middle Eastern infants being 214.3 g lighter (95% CI –33.7 g to –395.0 g, $P = 0.02$) relative to Swiss infants. Inclusion of gestational diabetes in the model did not change the results.

Among the study participants, 29.7% underwent caesarean section. To evaluate the relative odds for caesarean section, we conducted a multivariable logistic regression analysis (Table 4) (ethnic-cultural background as a categorical variable). Increased maternal age and pre-pregnancy BMI were significantly associated with increased odds of caesarean section ($P \leq 0.003$); but increased parity was significantly associated with reduced odds of caesarean section ($P = 0.001$). Each kilogram of net weight gain during pregnancy increased the odds of caesarean section significantly (OR 1.03, 95% CI 1.01 to 1.05, $P = 0.003$). The fact that the quadratic term of birth weight (birth weight × birth weight) was significant indicated that the odds of caesarean section increased at the lower and higher end of the birth weight spectrum (non-linear relationship). The former Yugoslavian Muslim women had a significantly lower odds of caesarean section (OR 0.63, 95% CI 0.41 to 0.96; $P = 0.03$) relative to Swiss women. For Turkish and the former Yugoslavia non-Muslim women a similarly reduced odds was observed, but the results were not statistically significant (OR 0.77, 95% CI 0.45 to 1.35; $P = 0.37$ and OR 0.66, 95% CI 0.39 to 1.13; $P = 0.13$, respectively). Sri Lankan mothers had an almost 1.5 times higher odds of caesarean section than Swiss mothers, but the result was not statistically significant (OR 1.46, 95% CI 0.96 to 2.22; $P = 0.078$). Inclusion of gestational diabetes in the model did not change the results.

The analysis of primiparous women (data not shown) showed the same results for the odds of caesarean section as the analysis based on the entire cohort.

TABLE 4. Multivariate Logistic Regression Analysis of Caesarean Section

	Odds Ratio	95% CI		*P* Value
BMI (kg/m^2)	1.05	1.02	1.08	0.003
Maternal age (years)	1.05	1.03	1.08	$<$ 0.001
Smoking status				
Non-smoking	Ref.			
Smoking	0.83	0.53	1.32	0.434
Parity	0.78	0.68	0.90	0.001
Net weight gain (kg)	1.03	1.01	1.05	0.003
Birthweight (kg)	0.002	0.0001	0.03	$<$ 0.001
Birthweight $\times$ birthweight (kg^2)	2.37	1.63	3.47	$<$ 0.001
Ethnic-cultural background				
Switzerland	Ref.			
North and East Europe	0.89	0.52	1.52	0.662
Southern Europe	1.29	0.82	2.04	0.269
F. Yugoslavia, non-Muslim	0.66	0.39	1.13	0.133
F. Yugoslavia, Muslim	0.63	0.41	0.96	0.030
Turkey	0.77	0.45	1.35	0.367
Sri Lanka	1.46	0.96	2.22	0.078
Middle East	0.41	0.13	1.27	0.124
South Asia	1.02	0.47	2.19	0.968
Far East	1.05	0.48	2.27	0.911
Latin America	1.05	0.56	1.99	0.871
Africa	1.11	0.67	1.84	0.681

DISCUSSION

In this diverse cohort of live-born and full-term infants, we found a wide range of pre-pregnancy maternal BMI, and BMI varied substantially by ethnic-cultural backgrounds. Anthropometry varies by ethnicity, geography and food availability (WHO, 1995b). However, we found a larger than expected, almost 18 fold, difference in prevalence of overweight from 2.8% in Far Eastern Asian mothers to 50% in African

mothers. Overweight is increasing in Europe among native (Forsum, Bostrom, Eriksson, & Olin-Skoglund, 2003; Heitmann, 2000) and immigrant populations (Holvik, Meyer, Haug, & Brunvand, 2005; Wandell, Ponzer, Johansson, Sundquist, & Sundquist, 2004), including women of childbearing age from different ethnic-cultural backgrounds (Roville-Sausse, Truc, & Jacob, 2001; Vahratian et al., 2004). A previous Swiss study reported that 20% of women between 18 and 40 years had BMIs above 25 (Eichholzer & Camenzind, 2003), but no data are available on the nationality of these women. To our knowledge, this is the first report of ethnic differences in overweight and obesity in women of childbearing age in Switzerland.

Given that high pre-pregnant BMI negatively influences pregnancy outcomes (Brawarsky, Stotland, Jackson, Fuentes-Afflick, Escobar, Rubashkin, & Haas, 2005; Cogswell, Perry, Schieve, & Dietz, 2001; Dietz et al., 2005), our findings that ethnic-cultural background was strongly associated with overweight suggests a need to provide culturally appropriate interventions, such as nutritional and behavioral counseling, including information on physical activity to encourage healthy body size before and during pregnancy (Abrams, Altman, & Pickett, 2000; Anderson, 2001; Siega-Riz & Laraia, 2006).

In the unadjusted comparison, infant birth weights of immigrant Sri Lankan and Middle Eastern mothers were on average over 110 g lighter than Swiss infants (Sri Lanka 3,264 g, Middle East 3,256 g, Swiss 3,376 g). In contrast, the mean birth weight of infants born in Sri Lanka was 2,841 g (SD 458 g) (WHO, 1995a). For Middle Eastern infants no such data were available. The reason that Sri Lankan infants born in Switzerland were smaller than Swiss infants, but heavier than infants born in their home country, is probably owing to a "healthy immigrant effect." This "healthy immigrant effect" theory postulates that those who can afford to emigrate, are mostly younger and usually have a better health status than the home population (Wingate & Alexander, 2006). Good health behavior is usually continued in the country of adoption for a couple of years (Guendelman et al., 1999).

Nonetheless, after controlling for potential confounding covariates, the Middle Eastern infants in this study were 214 g and the Sri Lankan infants were 145 g lighter than Swiss infants. One other study in France also found lower birth weight in infants of immigrant Sri Lankan mothers compared with French mothers (Roville-Sausse, Truc, & Jacob, 2001). A Swedish study showed a higher small-for-gestational age rate for Middle Eastern and North African infants than Swedish infants (Dejin-Karlsson & Ostergren, 2004). Only 2% of infants in our entire

cohort had a birth weight below 2,500 g, and neither Sri Lankan nor Middle Eastern infants were overrepresented in this low-birth-weight group. Nevertheless, it would be useful to know whether this lower birth weight is reflected in poorer neonatal health. This will have to be investigated elsewhere as all the infants included in this study were healthy live-born infants at term.

In our study, each unit increase in pre-pregnancy BMI and net weight gain was associated with significantly higher odds of caesarean section, even after controlling for confounding factors. A remarkably lower odds of caesarean section was observed in Muslim mothers from the former Yugoslavia. A trend for lower odds was also seen in non-Muslim mothers from the former Yugoslavia, as well as in Turkish mothers, where as we found higher odds for caesarean section in Sri Lankan mothers (despite their small neonates), but the difference in odds did not reach statistical significance in those groups. Differences of odds of caesarean section have been linked to various factors: different or inadequate labor management and different maternal knowledge and attitudes towards labor in immigrant groups, ability to cope with pain associated with labor and family support, particularly female family support as labor companions, emotional and traditional beliefs, physical components as pain medication and duration of labor, as well as body shapes, distribution of fat and connective tissue (Diani et al., 2003; Green & Baston, 2003; Ibison, 2005; Johnson, Lewis, & Ansell, 1995; Vangen et al., 2000; Woollett, Dosanjh, Nicolson, Marshall, Djhanbakhch, & Hadlow, 1995). Language problems are controversially discussed.

Yoong et al. (Yoong, Wagley, Fong, Chukwuma, & Nauta, 2004) have investigated Kosovo Albanian asylum seekers in the UK who are almost equivalent in ethnic-cultural background to the former Yugoslavian Muslim women in the present study. The authors did not find a difference in occurrence of caesarean section between these asylum seekers and the host population. They also related good family support as well as low intake of alcohol and nicotine in this immigrant group to the lack of difference in occurrence of caesarean section.

Nevertheless, the overall caesarean section rate of 29.7% in our study reflects some selection bias, since the hospital from which rates were obtained was a tertiary facility and an educational hospital. During our study period, the overall rate for caesarean section in Switzerland rose from 26.3% in 2001 to 29.2% in 2003 reflecting a general worldwide trend.

Our classification of ethnic-cultural background has not been used elsewhere, but like other European studies, we separated the mother/infant pairs by the most frequently encountered immigrant groups

(Guendelman et al., 1999; Margetts et al., 2002; Roville-Sausse, Truc, & Jacob, 2001). Therefore, groups of immigrant women represented under labels such as "Latin American" or "African" are heterogeneous, and some categories contained insufficient numbers to attain the statistical power to detect differences.

In addition to the limitations described above relating to the definition of ethnic-cultural background and need to combine diverse groups owing to low numbers, as well as lack of data on behavior and attitude, the study had several others. The selection of the study participants could have been biased owing to inclusion of participants from only a tertiary center. To reduce selection bias, we included only pregnant women who were seen every trimester and therefore, were not referred to the hospital later in pregnancy, confounding the cohort with high risk patients. Including only a small analytic sample, by excluding a large number of women who were not seen regularly for prenatal care ensured equal care and minimized recall bias for pre-pregnancy weight, but may have reduced generalizability of the results. In addition, caesarean section in a prior pregnancy might have influenced mode of delivery in a subsequent pregnancy. Our separate analysis of nulliparous women for the odds of caesarean section showed the same results as observed in the whole cohort, confirming minimal confounding because of caesarean section in prior pregnancies. Self-reported data may have limited validity, but, in general, self-reported weights correlate well with measured weights (Harris & Ellison, 1998). Nevertheless, we have no information how well non-Swiss women recalled their pre-pregnancy weights; hence including women in the first trimester enhanced the reliability, since not much time has passed, but excluded a large proportion of women which may have enhanced selection bias, as indicated already.

In summary, overweight is in this cohort related to adverse pregnancy outcomes in certain ethnic-cultural groups. Our data suggest that Sri Lankan and Middle Eastern mothers in particular had increased odds for lower birth weight and might be groups of women that should be further investigated to clarify these differences. The former Yugoslavian mothers had significantly lower odds of caesarean section compared with Swiss mothers. Further studies will be needed to determine whether factors such as nutrition and other behaviors influence the relationships among ethnic-cultural backgrounds, BMI and birth weight as well as caesarean section in the increasingly diverse environment of prenatal care in European countries.

REFERENCES

Abrams, B., Altman, S.L., & Pickett, K.E. (2000). Pregnancy weight gain: Still controversial. *Am J Clin Nutr*, 71(Suppl. 5), 1233S-1241S.

Ahlqvist, M. & Wirfalt, E. (2000). Beliefs concerning dietary practices during pregnancy and lactation. A qualitative study among Iranian women residing in Sweden. *Scand J Caring Sci*, 14(2), 105-111.

Anderson, A.S. (2001). Symposium on "nutritional adaptation to pregnancy and lactation." Pregnancy as a time for dietary change? *Proc Nutr Soc*, 60(4), 497-504.

Brawarsky, P., Stotland, N.E., Jackson, R.A., Fuentes-Afflick, E., Escobar, G.J., Rubashkin, N., & Haas, J.S. (2005). Pre-pregnancy and pregnancy-related factors and the risk of excessive or inadequate gestational weight gain. *Int J Gynaecol Obstet*, 91(2), 125-131.

Buekens, P., Masuy-Stroobant, G., & Delvaux, T. (1998). High birthweights among infants of north African immigrants in Belgium. *Am J Public Health*, 88(5), 808-811.

Cogswell, M.E., Perry, G.S., Schieve, L.A., & Dietz, W.H. (2001). Obesity in women of childbearing age: Risks, prevention, and treatment. *Prim Care Update Ob Gyns*, 8(3), 89-105.

Columbia University (2001). *The Columbia Encyclopedia.* http://www.bartleby.com/65/

Dejin-Karlsson, E. & Ostergren, P.O. (2004). Country of origin, social support and the risk of small for gestational age birth. *Scand J Public Health*, 32(6), 442-449.

Diani, F., Zanconato, G., Foschi, F., Turinetto, A., & Franchi, M. (2003). Management of the pregnant immigrant woman in the decade 1992-2001. *J Obstet Gynaecol*, 23(6), 615-617.

Dietz, P.M., Callaghan, W.M., Morrow, B., & Cogswell, M.E. (2005). Population-based assessment of the risk of primary cesarean delivery due to excess pre-pregnancy weight among nulliparous women delivering term infants. *Matern Child Health J*, 9(3), 237-244.

Eaton, P.M., Wharton, P.A., & Wharton, B.A. (1984). Nutrient intake of pregnant Asian women at Sorrento Maternity Hospital, Birmingham. *Br J Nutr*, 52(3), 457-468.

Eichholzer, M. & Camenzind, E. (2003). Overweight, obesity and underweight in Switzerland: Results of the 2000 Nutri-Trend Study. *Schweiz Rundsch Med Prax*, 92(18), 847-858.

Festini, F., Reali, M.F., Taccetti, G., Repetto, T., & de Martino, M. (2004). Birth weight of Chinese babies born in Italy. *Arch Dis Child Fetal Neonatal Ed*, 89(2), F187.

Forsum, E., Bostrom, K., Eriksson, B., & Olin-Skoglund, S. (2003). A woman's weight before and during pregnancy is of importance to her infant. USA guidelines would benefit public health in Sweden. *Lakartidningen*, 100(48), 3954-3958.

Green, J.M. & Baston, H.A. (2003). Feeling in control during labor: Concepts, correlates, and consequences. *Birth*, 30(4), 235-247.

Guendelman, S., Buekens, P., Blondel, B., Kaminski, M., Notzon, F.C., & Masuy-Stroobant, G. (1999). Birth outcomes of immigrant women in the United States, France, and Belgium. *Matern Child Health J*, 3(4), 177-187.

Harris, H.E. & Ellison, G.T. (1998). Practical approaches for estimating prepregnant body weight. *J Nurse Midwifery*, 43(2), 97-101.
Heitmann, B.L. (2000). Ten-year trends in overweight and obesity among Danish men and women aged 30-60 years. *Int J Obes Relat Metab Disord*, 24(10), 1347-1352.
Holvik, K., Meyer, H.E., Haug, E., & Brunvand, L. (2005). Prevalence and predictors of vitamin D deficiency in five immigrant groups living in Oslo, Norway: The Oslo Immigrant Health Study. *Eur J Clin Nutr*, 59(1), 57-63.
Ibison, J.M. (2005). Ethnicity and mode of delivery in "low-risk" first-time mothers, East London, 1988-1997. *Eur J Obstet Gynecol Reprod Biol*, 118(2), 199-205.
Institute of Medicine (1990). *Nutrition during Pregnancy: Part I: Weight gain, Part II: Nutrient Supplements*. Washington, DC: National Academy of Sciences.
Johnson, N.P., Lewis, J., & Ansell, D.A. (1995). Does ethnicity influence obstetric intervention? *N Z Med J*, 108(1013), 511-512.
Laczko, F. (2002). New directions for migration policy in Europe. *Philos Trans R Soc Lond B Biol Sci*, 357(1420), 599-608.
Margetts, B.M., Mohd Yusof, S., Al Dallal, Z., & Jackson, A.A. (2002). Persistence of lower birth weight in second generation South Asian babies born in the United Kingdom. *J Epidemiol Community Health*, 56(9), 684-687.
Perucchini, D., Fischer, U., Spinas, G.A., Huch, R., Huch, A., & Lehmann, R. (1999). Using fasting plasma glucose concentrations to screen for gestational diabetes mellitus: Prospective population based study. *BMJ*, 319(7213), 812-815.
Roville-Sausse, F., Truc, J.B., & Jacob, D. (2001). Maternal weight gain during pregnancy in various immigrant communities living in France. *Rev Epidemiol Sante Publique*, 49(5), 439-447.
Siega-Riz, A.M. & Laraia, B. (2006). The implications of maternal overweight and obesity on the course of pregnancy and birth outcomes. *Matern Child Health J*, 10 (Suppl. 7), 153-156.
Vahratian, A., Buekens, P., Delvaux, T., Boutsen, M., Wang, Y., & Kupper, L.L. (2004). Birthweight differences among infants of North African immigrants and Belgians in Belgium. *Eur J Public Health*, 14(4), 381-383.
Vangen, S., Stoltenberg, C., Skrondal, A., Magnus, P., & Stray-Pedersen, B. (2000). Cesarean section among immigrants in Norway. *Acta Obstet Gynecol Scand*, 79(7), 553-558.
Vangen, S., Stoltenberg, C., Skjaerven, R., Magnus, P., Harris, J.R., & Stray-Pedersen, B. (2002). The heavier the better? Birthweight and perinatal mortality in different ethnic groups. *Int J Epidemiol*, 31(3), 654-660.
Wandell, P.E., Ponzer, S., Johansson, S.E., Sundquist, K., & Sundquist, J. (2004). Country of birth and body mass index: A national study of 2,000 immigrants in Sweden. *Eur J Epidemiol*, 19(11), 1005-1010.
Wharton, P.A., Eaton, P.M., & Wharton, B.A. (1984). Subethnic variation in the diets of Moslem, Sikh and Hindu pregnant women at Sorrento Maternity Hospital, Birmingham. *Br J Nutr*, 52(3), 469-476.
WHO (1995a). *Sri Lanka*, Country Profile: WHO.
WHO (1995b). Maternal anthropometry and pregnancy outcomes. A WHO Collaborative Study. *Bull World Health Organ*, 73 (Suppl.), 1-98.

Wingate, M.S. & Alexander, G.R. (2006). The healthy migrant theory: Variations in pregnancy outcomes among US-born migrants. *Soc Sci Med*, 62(2), 491-498.

Woollett, A., Dosanjh, N., Nicolson, P., Marshall, H., Djhanbakhch, O., & Hadlow, J. (1995). The ideas and experiences of pregnancy and childbirth of Asian and non-Asian women in east London. *Br J Med Psychol*, 68 (Pt 1), 65-84.

Yoong, W., Wagley, A., Fong, C., Chukwuma, C., & Nauta, M. (2004). Obstetric performance of ethnic Kosovo Albanian asylum seekers in London: A case-control study. *J Obstet Gynaecol*, 24(5), 510-512.

doi:10.1300/J013v45n02_02

5.2 Publication II

Richard A, Rohrmann S, **Quack Loetscher KC** (2017)

Prevalence of vitamin D deficiency and its associations with skin color in pregnant women in the first trimester in a sample from Switzerland.

Nutrients. March 10;9(3)

nutrients

MDPI

Article

Prevalence of Vitamin D Deficiency and Its Associations with Skin Color in Pregnant Women in the First Trimester in a Sample from Switzerland

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Received: 29 January 2017; Accepted: 6 March 2017; Published: 10 March 2017

Abstract: Vitamin D deficiency in pregnancy has negative clinical consequences, such as associations with glucose intolerance, and has been shown to be distributed differently in certain ethnic groups. In some countries, a difference in the rate of vitamin D deficiency was detected in pregnant women depending on their skin color. We examined the prevalence of vitamin D deficiency (<20 ng/mL) in women in early pregnancy in Switzerland and evaluated the association of skin color with vitamin D deficiency. In a single-center cohort study, the validated Fitzpatrick scale and objective melanin index were used to determine skin color. Of the 204 pregnant women included, 63% were vitamin D deficient. The mean serum 25-hydroxyvitamin D concentration was 26.1 ng/mL (95% confidence interval (CI) 24.8–27.4) in vitamin D–sufficient women and 10.5 ng/mL (95% CI 9.7–11.5) in women with deficiency. In the most parsimonious model, women with dark skin color were statistically significantly more often vitamin D deficient compared to women with light skin color (OR 2.60; 95% CI 1.08–6.22; adjusted for age, season, vitamin D supplement use, body mass index, smoking, parity). This calls for more intense counseling as one policy option to improve vitamin D status during pregnancy, i.e., use of vitamin D supplements during pregnancy, in particular for women with darker skin color.

Keywords: vitamin D; pregnancy; skin color; vitamin D deficiency; Switzerland

1. Introduction

During the last century, vitamin D fortification programs have largely eradicated the health risks of vitamin D deficiency such as rickets and osteomalacia from western populations. However, vitamin D deficiency (<20 ng/mL) is reemerging and suboptimal vitamin D blood levels are widespread in industrialized nations, specifically in women with darker skin color [1–7]. A suboptimal vitamin D level is thought to be associated with a range of diseases such as cardiovascular disease and diabetes [8] as well as with the risk of several types of cancer or depression [9,10]. Cholecalciferol (vitamin D3) is synthesized in the skin by sunlight (UVB) from 7-dehydrocholesterol, followed by transformation to the active form 25-hydroxyvitamin D ((25(OH)D) in the liver. In a further step, 25(OH)D is metabolized into the physiologically active 1,25-dihydroxyvitamin D (1,25(OH)2D) in the kidney. As 25(OH)D has a half-life of 15 days, which is longer than that of 1,25(OH)2D, it is considered to be the better indicator of vitamin D status. Individuals living in countries with less sun exposure might be at higher risk for vitamin D deficiency [11]. Additionally, during winter and spring, sun exposure is low in northern countries. Besides geographic and weather circumstances, several studies showed that personal characteristics affect vitamin D synthesis. Circulating vitamin D concentrations differ by skin color: Individuals with darker skin produce less vitamin D with the same amount of sunlight exposure

than individuals with lighter skin color [10,12]. In Europe, estimated vitamin D levels showed a large variation due to risk factors such as immigration from countries with higher sun exposure, low consumption of foods rich in vitamin D or low vitamin D supplementation [13].

In pregnancy, increased calcium and adequate vitamin D levels are required and, thus, pregnant women are, in general, at higher risk of vitamin D deficiency [6]. Vitamin D deficiency in pregnancy has been shown to be associated with a variety of clinical consequences [14–17] that range from a negative influence on glucose tolerance to an association with preeclampsia. Vitamin D supplementation can improve birth weight in certain ethnic groups [18].

Currently, the vitamin D status of pregnant women living in Switzerland is unknown [19] and, hence, the aim of our study was to evaluate vitamin D levels in pregnant women and to determine the prevalence of vitamin D deficiency. Furthermore, we aimed to address the question of whether the prevalence of vitamin D deficiency differs between women with light or dark skin color, i.e., between specific subgroups of the population living in Switzerland.

2. Materials and Methods

2.1. Study Population

Between September 2014 and December 2015, 80% of the women visiting the Clinic of Obstetric at the University Hospital Zurich for their first pregnancy visit in the first trimester were recruited for participation in this vitamin D study. The study was approved by the ethics committee of the canton of Zurich, Switzerland (KEK-ZH-Nr. 2013-0213). Exclusion criteria were twin pregnancy, HIV, history of parathyroid, renal or liver disease, chronic malabsorption syndromes or granuloma-forming disorders, age below 18 years or known or suspected drug or alcohol abuse, because they may alter vitamin D metabolism. We collected data of 205 women. Due to one missing information on vitamin D status, our final sample consisted of 204 women.

2.2. Vitamin D Blood Samples

After giving informed consent, a blood sample of 10 mL was collected during the routine blood collection of the pregnancy examination. Blood samples were centrifuged and serum was extracted in the Institute of Clinical Chemistry at the University Hospital Zurich within hours after blood sampling. Total 25-hydroxyvitamin D was analyzed on the same day using the vitamin D total-analysis Roche Cobas® electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland). The method has a detection range of 3.0–70.0 ng/mL for 25(OH) vitamin D and a variation coefficient of 2.2%–6.8%.

Vitamin D deficiency was defined as 25(OH)D concentrations <20 ng/mL vs. sufficiency as $\geq$20 ng/mL as recommended by the Endocrine Society [20]. The conversion factor to the SI units (nmol/L) is 2.496.

2.3. Skin Color

The physician together with the participant filled out a questionnaire. The skin color of the women was assessed according to the classification by Fitzpatrick [21]. This scale allows for differentiating between skin phototypes based on skin reaction to sun exposure. The origin scale consists of six skin types (I to VI). We used an adapted scale, which converged type V (dark brown) and VI (black) into type V due to small numbers in these groups. The classification of skin type was assessed first by showing the participant a picture of the different skin color types (I–IV) and second, by asking on what happens to the untanned skin if it is exposed in the early summer at noon for 45 to 60 min to the sun. Answers varied from (I) "painful sunburn after 24 h and not tanned after one week"; (II) "painful sunburn after 24 h and minimally tanned after one week"; (III) "minimal sunburn after 24 h and uniformly tanned after one week"; (IV) "no sunburn after 24 h and tanned after one week" to (V) "Skin is deeply pigmented brown/black, no sunburn and tanned after one week". Based on the pictures and questions the women estimated their own skin phototype. Additionally, the interviewer evaluated the

skin type. When the classification of pregnant woman and the interviewer disagreed, the rounded arithmetic mean of was used to determine the skin color type. Skin color type was dichotomized into Fitzpatrick scale I to III vs. IV and V.

Furthermore, the skin type was measured with a DSM II ColorMeter (Cortex Technology, Hadsund, Denmark) resulting in a melanin index [22]. The device is a narrow band spectroscopy instrument with a green diode centered on 568 nm and red diode centered on 655 nm. The device was calibrated every week with white balance. Melanin index was measured 3 times on the inner underarm and the arithmetic mean was calculated to categorize melanin in quartiles. Spearman correlation coefficient between melanin index and the Fitzpatrick index was 0.65.

2.4. Covariates

Based on the World Bank Map, country of a woman's origin (place of birth) was grouped into five categories; (1) Switzerland and Germany; (2) Northern America, Northern Europe, Caucasus, Central Asia and New Zealand; (3) Southern Europe, Australia, Latin America and the Caribbean; (4) South- and East Asia and Pacific; and (5) Africa and Middle East. For further analyses these countries were dichotomized into groups 1 and 2 vs. groups 3–5. Further covariates were age, week of pregnancy, parity, gravidity, body mass index (BMI) before pregnancy, actual BMI, educational level of the pregnant woman and her partner (less than compulsory education vs. low (compulsory education) vs. middle (secondary education) vs. high (tertiary education)), smoking status (never vs. former vs. current), season of blood collection (winter vs. spring vs. summer vs. fall), number of days per week spent at least 1 hour outdoors in the past half year, sun protection (never vs. sometimes vs. always), fish consumption (only salmon, tuna, mackerels and herring; at least once per week vs. less), vitamin D supplements intake as recommended 500 IE daily (yes vs. no).

In addition, maternal age, parity, week of pregnancy, body mass index (BMI) before pregnancy and weight gain till the first visit were collected from medical records.

2.5. Statistical Analyses

All statistical analyses were conducted using STATA software version 13.1 (College Station, TX, USA). Geometric means and corresponding 95% confidence intervals (CI) were used to illustrate the differences in vitamin D concentrations between light- and dark-skinned individuals.

Logistic regression analyses were used to determine associations of skin color with vitamin D deficiency. The Akaike Information Criteria (AIC) was used for selecting the final model solution for multivariable adjustment. As a result of the AIC and of dropping variables because of collinearity, we presented the 4 most parsimonious models; (1) adjusted for age; (2) adjusted for age and season, (3) adjusted for age, season, vitamin D supplement intake, BMI and smoking status; and (4) adjusted for age, season, vitamin D supplement intake, BMI, smoking status and parity. Sensitivity-analyses were performed using the dichotomized countries of origin and the dichotomized melanin index (by median) instead of the Fitzpatrick scale. Differences between groups were examined using Anova and *t*-test ($p < 0.05$, two-sided).

3. Results

Descriptive characteristics of the 204 women are provided in Table 1 for women with and without vitamin D deficiency. A description by skin type can be found in Supplementary Table S1.

Table 1. General characteristics of pregnant women by vitamin D status.

Variables of Interest	Vitamin D Sufficiency [1]	Vitamin D Deficiency [2]	*p*-Value [5]
n (%)	75 (37)	129 (63)	
25(OH)D ng/mL, geometric mean (95% CI)	26.1 (24.8–27.4)	10.5 (9.7–11.5)	<0.001
Light skin color [3], %	88	67	<0.05
Melanin levels, median (Q1, Q3)	32.9 (30.8, 37.2)	34.3 (30.8, 41.8)	0.07
Age, mean (SD)	31.1 (4.8)	29.4 (4.8)	<0.05
Week of pregnancy, median (Q1, Q3)	9 (8, 10)	9 (8, 10)	0.39
Parity, % nulliparous	55	52	0.32
Gravidity, % first pregnancy	43	40	0.11
BMI (kg/m^2) before pregnancy, median (Q1, Q3)	20.7 (19.7, 23.1)	22.5 (20.4, 25.3)	<0.05
BMI (kg/m^2) current, median (Q1, Q3)	21.5 (20.1, 23.9)	22.8 (20.7, 26.2)	<0.05
Country of origin, %			
Switzerland and Germany	35	14	
North America, North Europe, Caucasus, Central Asia and New Zealand (without Switzerland and Germany)	28	15	
South Europe, Australia, Latin America and the Caribbean	28	29	
South-, East Asia and Pacific	5	22	
Africa and Middle East	4	22	<0.001
Educational level achieved [4], %			
less than compulsory education	3	8	
low education	4	16	
middle education	35	33	
high education	59	44	<0.05
Educational level achieved of the partner [4], %			
less than compulsory education	4	8	
low education	3	14	
middle education	33	43	
high education	60	35	0.001
Smoking status, %			
Never smoker	47	67	
Ever smoker	45	22	
Current smoker	8	12	<0.05
Season			
Winter	24	25	
Spring	19	23	
Summer	20	19	
Fall	37	33	0.90
Days per week spent at least 1 h outdoor in the past half year, median (Q1, Q3)	2 (2, 5)	3 (2, 7)	0.44
Using sun protection in summer, %			
Never	13	31	
Sometimes	51	31	
Always	36	38	<0.05
Fish consumption at least once per week, %	51	45	0.41
Vitamin D supplement intake, %	9	9	0.97

[1] 25(OH)D $\geq$ 20 ng/mL; [2] 25(OH)D < 20 ng/mL; [3] Light skin color defined as values I to III from the Fitzpatrick scale; [4] Low = compulsory education; middle = secondary education; high = tertiary education; [5] *t*-test was used for means, Mann-Whitney for medians. Chi^2 was used for proportions or Fisher's exact test, when one cell was <5.

Almost two-thirds of the women were vitamin D deficient. The mean serum vitamin D concentration was 26.1 ng/mL in vitamin D–sufficient women and 10.5 ng/mL in women with deficiency. Light skin color was reported by 88% of the women with sufficient vitamin D levels and by 66.6% with vitamin D deficiency.

The mean age at blood collection was 31.1 and 29.4 years in vitamin D–sufficient and –deficient women, respectively. About one-third of the women with sufficient vitamin D levels and 14% of vitamin D–deficient women were of German or Swiss origin. Half of the women with a sufficient vitamin D concentration sometimes used sun protection, 13% never used it and 36% always used sun protection. In women with vitamin D deficiency, sun protection was used "never", "sometimes" or "always" by one-third of women each. Fish consumption was reported by 51% of the women without and by 45% of the women with vitamin D deficiency, and vitamin D supplements intake was reported by 9% of the women without and with vitamin D deficiency, respectively.

The associations of dark skin color with vitamin D deficiency were assessed by logistic regression using different adjustment models (Table 2).

Table 2. Associations between skin color and vitamin D deficiency in 204 pregnant women (reference: vitamin D level $\geq$ 20 ng/mL).

Dark Skin Color	OR	95% CI	AIC
age adjusted model	3.25	(1.46, 7.24)	259
age and season adjusted	3.29	(1.47, 7.36)	264
multivariable adjusted model [1]	2.56	(1.08, 6.11)	266
multivariable adjusted model [2]	2.60	(1.08, 6.22)	268

[1] Adjusted for age, season, vitamin D supplement intake, BMI, smoking status; [2] Adjusted for age, season, vitamin D supplement intake, BMI, smoking status, parity.

The AIC fit best for the age-adjusted model with an OR of 3.25 (95% CI 1.46–7.24) for the associations of skin color with vitamin D deficiency. The next model with a good AIC fit included age and season (OR 3.29; 95% CI 1.4–7.36). In the multivariable adjusted model including age, season, vitamin D supplement intake, BMI, smoking status and parity, the OR was 2.60 (95% CI 1.08–6.22). In the sensitivity analysis using dichotomized countries of origin instead of the Fitzpatrick scale, the best AIC fit and the results remained similar (Supplementary Table S2). However, in the sensitivity analysis with the dichotomized melanin index as a proxy for skin color, the AIC fit best for the same model as in our main analysis, but the associations of dark skin color with vitamin D deficiency were attenuated and the results for models 3 and 4 did not remain statistically significant (Supplementary Table S3).

According to the results of the AIC, age and season explained the model best. Figure 1 depicts the geometric mean vitamin D levels by light and dark skin color type (according to the Fitzpatrick scale) stratified by season.

Women with light skin color had the highest vitamin D levels in summer and the lowest in winter (18.4 ng/mL (95% CI 15.0–22.7) and 14.6 ng/mL (95% CI 12.3–17.4), respectively). For women with dark skin color, these levels in summer and winter were lower (12.9 ng/mL (95% CI 8.5–19.6) and 7.6 ng/mL (95% CI 4.6–12.5), respectively). However, differences between seasons were not statistically significant either in light-skinned or in dark-skinned women.

Younger women had lower vitamin D levels compared to older women with light and with dark skin color (Figure 2).

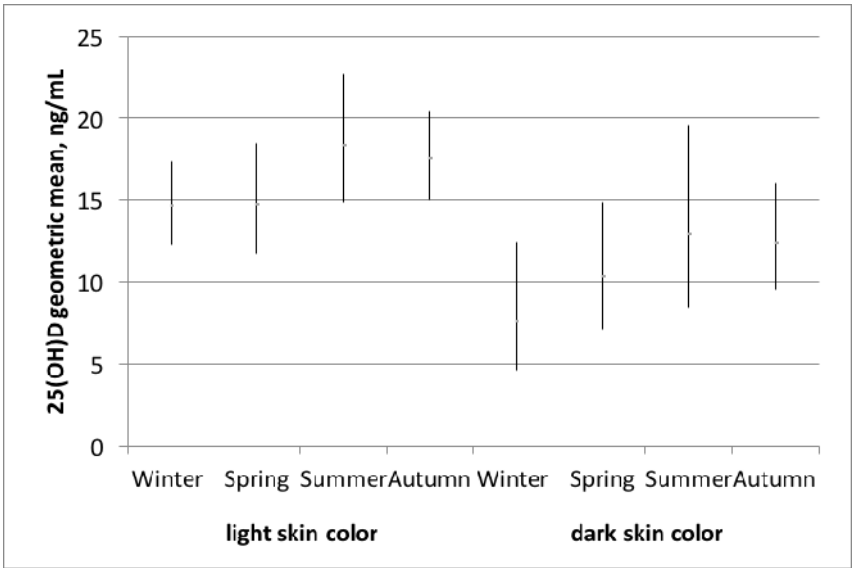

Figure 1. Vitamin D levels stratified by light and dark skin color and season according to the Fitzpatrick scale (I, II, III vs. IV, V) and season (winter = December–February, spring = March–May, summer = June–August, autumn = September–November).

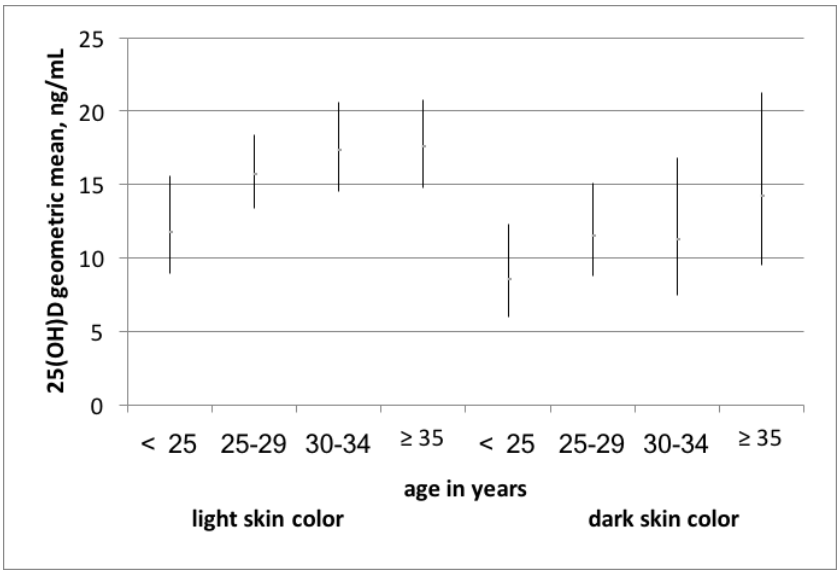

Figure 2. Vitamin D levels stratified by light and dark skin color according to the Fitzpatrick scale and the four age groups.

Vitamin D levels in women younger than 25 years were 11.8 ng/mL (95% CI 8.9–15.6) and 8.6 ng/mL (95% CI 6.0–12.3) in light and dark skin color, respectively. Women aged 35 or above had a mean vitamin D level of 17.6 ng/mL (95% CI 14.8–20.8) (light skin color) and 14.2 ng/mL (95% CI 9.5–21.9) (dark skin color). In dark-skinned women, differences were not statistically significant; in light-skinned women, the *p*-value was 0.06 (Anova).

4. Discussion

In our study, almost two-thirds of the pregnant women were vitamin D deficient and dark skin color was associated with a higher prevalence of vitamin D deficiency. This prevalence is almost twice as high as in the normal population (38%) [23].

To our knowledge, the prevalence of vitamin D deficiency in women in the first trimester of pregnancy has not yet been evaluated in Switzerland. A recent systematic review looking at vitamin D deficiency in pregnant women in the Mediterranean region observed a prevalence of vitamin D deficiency (defined as ≤20 ng/mL) in pregnant women ranging from 22.7% to 90.3% [24]. Only four out of 15 studies included in the systematic review were conducted during the first trimester of pregnancy, with a vitamin D deficiency prevalence ranging from 22.7% to 59% [25–28]. Studies conducted in northern European countries or the US also reported heterogeneous rates of vitamin D deficiency, such as 10% in US in women in early pregnancy or 65% in pregnant women in Sweden (levels <50 nmol/L, which corresponds to ≤20 ng/mL). In Belgium, 47% of pregnant women in the first trimester were vitamin D deficient [29], in the Netherlands 8%–62% in the 12th week of pregnancy were deficient (deficiency defined as <25 nmol/L) [30], and in Norway 77.4% of pregnant women in the first trimester had a vitamin D deficiency [31]. Thus, our result lies within the range of vitamin D deficiency observed in early pregnancy.

Concerning skin color, our results concur with previous data [30,32–34] showing that vitamin D deficiency varies by light and dark skin phototypes, i.e., dark skin color was significantly associated with vitamin D deficiency. Furthermore, studies consistently show that vitamin D levels among pregnant women in northern Europe and the US are lower in ethnic minority groups, which generally have darker skin. Dark-skinned individuals produce less 25(OH)D than individuals with light skin with the same sunlight exposure (UVB) [30,35–37].

Endogenous skin synthesis through UVB radiation and diet (or vitamin D supplement intake, respectively) are the two main sources of vitamin D. In our study, adjusting for season showed the best model fit, expressed as AIC (including also age as a covariate), which serves as a proxy for sunlight. Looking in more detail into vitamin D levels stratified by skin color and seasons, women in our study had higher vitamin D levels in summer compared to winter, and vitamin D levels were lower in women with dark than with light skin color, but differences between seasons were not statistically significant. Previous studies described lower vitamin D levels in winter for the general population [35], and for pregnant women most studies found higher vitamin D levels in summer than in winter, but not all tested for statistical significance [6,38–40].

In our study only a small percentage of women took vitamin D supplements and only half of the women ate fish at least once per week. As vitamin D supplement intake was a good AIC model fit, vitamin D levels stratified by intake and skin color were examined but differences were not statistically significant (Supplementary Figure S1). A recent meta-analysis and a systematic review observed that supplementing pregnant women with vitamin D leads to higher levels of vitamin D at term [41,42]. We hypothesize that in our study, it might be too early in pregnancy to see an effect. From a public health perspective, fortification of food could improve vitamin D levels in all pregnant women. To date, vitamin D fortification of food is more common in northern Europe (e.g., Norway, Denmark and Sweden) than in other countries of Europe, such as Switzerland [43].

We observed that age was an important covariate and that vitamin D levels were higher in older compared to younger pregnant women, although differences were not significant. Results of other studies looking at the relationship between age and vitamin D are contradictory and no association, non-linear association [44], or similar results as in our study [45] were observed. A possible explanation for an association with age may be that older individuals are more health conscious than younger pregnant women.

In our analysis, we used three different variables to categorize by skin type, namely the Fitzpatrick scale, melanin index and country of origin, and we observed that either variable was a predictor of vitamin D deficiency. However, the association of the (dichotomized) melanin index and vitamin D deficiency was strongly attenuated after adjusting for vitamin D supplement intake, BMI, and smoking status in addition to age and season. It might be that, despite the strong correlation between the melanin index and Fitzpatrick scale, the dichotomizing melanin index is less able to capture the extremes of skin color than the dichotomizing Fitzpatrick scale.

Women included in the study came from a great variety of countries of origin, which allowed different skin pigmentation colors to be represented. A further strength was the inclusion of a variety of confounders in our study, but due to collinearity, such as from country of origin, and the melanin index with light and dark skin color according to the Fitzpatrick scale, we could not include these variables in our final multivariable adjusted models. Nevertheless, we performed sensitivity analyses with these variables, which mostly confirmed our results with the Fitzpatrick scale. A further limitation was that women with dark skin (Fitzpatrick scale V) were limited in number and that other factors that affect vitamin D levels were not assessed, such as veiling of the women or physical activity. Hence, the observation of non-statistically significant differences in our population might be due to small numbers. Finally, we included only one hospital in our analysis, which limits the generalizability of our results. However, women attending our clinical pregnancy controls came from the general population. Also, residual confounding cannot be ruled out.

5. Conclusions

The prevalence of vitamin D deficiency is common in women in early pregnancy. Almost two-thirds of all women in our study population had a vitamin D deficiency. To our knowledge, this is the first study that assessed prevalence rates for pregnant women in the Zurich area of Switzerland. We found a difference in 25(OH) vitamin D levels and prevalence depending on maternal skin type, emphasizing a consequent screening and supplementation program for pregnant women, in particular for women with a darker skin type.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/9/3/260/s1, Figure S1: Vitamin D levels by light and dark skin color and vitamin D supplementation status, Table S1: General characteristics of pregnant women with light and dark skin color, Table S2: Association between dichotomized country of origin and vitamin D deficiency in 204 pregnant women, Table S3: Association between dichotomized melanin index and vitamin D deficiency in 204 pregnant women.

Acknowledgments: We thank the Swiss National Science Foundation for their support of this project (NRP69 grant 4069-145194). We thank Nina Pupikofer for data entry and all women who participated in this study.

Author Contributions: Katharina C. Quack Lötscher, Sabine Rohrmann and Aline Richard designed the study and planned the analyses. Katharina C. Quack Lötscher supervised the recruiting of participants. Aline Richard performed the analyses and prepared the first draft of the manuscript. All authors contributed to the interpretation of the data and edited the manuscript. Sabine Rohrmann supervised the study. All authors have approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Davies, J.H.; Reed, J.M.; Blake, E.; Mrcpch, M.P.; Jackson, A.A.; Clarke, N.M. Epidemiology of vitamin d deficiency in children presenting to a pediatric orthopaedic service in the uk. *J. Pediatr. Orthop.* **2011**, *31*, 798–802. [CrossRef] [PubMed]
2. Merewood, A.; Mehta, S.D.; Grossman, X.; Chen, T.C.; Mathieu, J.S.; Holick, M.F.; Bauchner, H. Widespread vitamin d deficiency in urban massachusetts newborns and their mothers. *Pediatrics* **2010**, *125*, 640–647. [CrossRef] [PubMed]
3. Ginde, A.A.; Sullivan, A.F.; Mansbach, J.M.; Camargo, C.A., Jr. Vitamin d insufficiency in pregnant and nonpregnant women of childbearing age in the united states. *Am. J. Obstet. Gynecol.* **2010**, *202*, 436.e1–436.e8. [CrossRef] [PubMed]
4. Ergur, A.T.; Berberoglu, M.; Atasay, B.; Siklar, Z.; Bilir, P.; Arsan, S.; Soylemez, F.; Ocal, G. Vitamin d deficiency in turkish mothers and their neonates and in women of reproductive age. *J. Clin. Res. Pediatr. Endocrinol.* **2009**, *1*, 266–269. [CrossRef] [PubMed]
5. Islam, M.Z.; Viljakainen, H.T.; Karkkainen, M.U.; Saarnio, E.; Laitinen, K.; Lamberg-Allardt, C. Prevalence of vitamin d deficiency and secondary hyperparathyroidism during winter in pre-menopausal bangladeshi and somali immigrant and ethnic finnish women: Associations with forearm bone mineral density. *Br. J. Nutr.* **2012**, *107*, 277–283. [CrossRef] [PubMed]

6. Bowyer, L.; Catling-Paull, C.; Diamond, T.; Homer, C.; Davis, G.; Craig, M.E. Vitamin d, pth and calcium levels in pregnant women and their neonates. *Clin. Endocrinol.* **2009**, *70*, 372–377. [CrossRef] [PubMed]
7. Nicolaidou, P.; Hatzistamatiou, Z.; Papadopoulou, A.; Kaleyias, J.; Floropoulou, E.; Lagona, E.; Tsagris, V.; Costalos, C.; Antsaklis, A. Low vitamin d status in mother-newborn pairs in greece. *Calcif. Tissue Int.* **2006**, *78*, 337–342. [CrossRef] [PubMed]
8. Holick, M.F. Vitamin d deficiency. *N. Engl. J. Med.* **2007**, *357*, 266–281. [CrossRef] [PubMed]
9. Tolppanen, A.M.; Sayers, A.; Fraser, W.D.; Lewis, G.; Zammit, S.; Lawlor, D.A. The association of serum 25-hydroxyvitamin d3 and d2 with depressive symptoms in childhood—A prospective cohort study. *J. Child Psychol. Psychiatry* **2012**, *53*, 757–766. [CrossRef] [PubMed]
10. Akeson, P.K.; Lind, T.; Hernell, O.; Silfverdal, S.A.; Ohlund, I. Serum vitamin d depends less on latitude than on skin color and dietary intake during early winter in northern europe. *J. Pediatr. Gastroenterol. Nutr.* **2016**, *62*, 643–649. [CrossRef] [PubMed]
11. Cadario, F.; Savastio, S.; Pozzi, E.; Capelli, A.; Dondi, E.; Gatto, M.; Zaffaroni, M.; Bona, G. Vitamin d status in cord blood and newborns: Ethnic differences. *Ital. J. Pediatr.* **2013**, *39*, 35. [CrossRef] [PubMed]
12. Clemens, T.L.; Adams, J.S.; Henderson, S.L.; Holick, M.F. Increased skin pigment reduces the capacity of skin to synthesise vitamin d3. *Lancet* **1982**, *1*, 74–76. [CrossRef]
13. Spiro, A.; Buttriss, J.L. Vitamin d: An overview of vitamin d status and intake in europe. *Nutr. Bull. BNF* **2014**, *39*, 322–350. [CrossRef] [PubMed]
14. Zhang, C.; Qiu, C.; Hu, F.B.; David, R.M.; van Dam, R.M.; Bralley, A.; Williams, M.A. Maternal plasma 25-hydroxyvitamin d concentrations and the risk for gestational diabetes mellitus. *PLoS ONE* **2008**, *3*, e3753. [CrossRef] [PubMed]
15. Bodnar, L.M.; Catov, J.M.; Simhan, H.N.; Holick, M.F.; Powers, R.W.; Roberts, J.M. Maternal vitamin d deficiency increases the risk of preeclampsia. *J. Clin. Endocrinol. Metab.* **2007**, *92*, 3517–3522. [CrossRef] [PubMed]
16. Halhali, A.; Diaz, L.; Avila, E.; Ariza, A.C.; Garabedian, M.; Larrea, F. Decreased fractional urinary calcium excretion and serum 1,25-dihydroxyvitamin d and igf-i levels in preeclampsia. *J. Steroid Biochem. Mol. Biol.* **2007**, *103*, 803–806. [CrossRef] [PubMed]
17. Halhali, A.; Tovar, A.R.; Torres, N.; Bourges, H.; Garabedian, M.; Larrea, F. Preeclampsia is associated with low circulating levels of insulin-like growth factor i and 1,25-dihydroxyvitamin d in maternal and umbilical cord compartments. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 1828–1833. [CrossRef] [PubMed]
18. Brooke, O.G.; Brown, I.R.; Bone, C.D.; Carter, N.D.; Cleeve, H.J.; Maxwell, J.D.; Robinson, V.P.; Winder, S.M. Vitamin d supplements in pregnant asian women: Effects on calcium status and fetal growth. *Br. Med. J.* **1980**, *280*, 751–754. [CrossRef] [PubMed]
19. Quack Lötscher, K. *Vitamin D and Pregnancy*; Federal Office for Public Health: Zurich, Switzerland, 2012.
20. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; Murad, M.H.; Weaver, C.M. Guidelines for preventing and treating vitamin d deficiency and insufficiency revisited. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 1153–1158. [CrossRef] [PubMed]
21. Fitzpatrick, T.B. The validity and practicality of sun-reactive skin types i through vi. *Arch. Dermatol.* **1988**, *124*, 869–871. [CrossRef] [PubMed]
22. Wagner, J.K.; Jovel, C.; Norton, H.L.; Parra, E.J.; Shriver, M.D. Comparing quantitative measures of erythema, pigmentation and skin response using reflectometry. *Pigment Cell Res. Spons. Eur. Soc. Pigment Cell Res. Int. Pigment Cell Soc.* **2002**, *15*, 379–384. [CrossRef]
23. Guessous, I.; Dudler, V.; Glatz, N.; Theler, J.M.; Zoller, O.; Paccaud, F.; Burnier, M.; Bochud, M.; Swiss Survey on Salt, G. Vitamin d levels and associated factors: A population-based study in switzerland. *Swiss Med. Wkly.* **2012**, *142*. [CrossRef] [PubMed]
24. Karras, S.; Paschou, S.A.; Kandaraki, E.; Anagnostis, P.; Annweiler, C.; Tarlatzis, B.C.; Hollis, B.W.; Grant, W.B.; Goulis, D.G. Hypovitaminosis d in pregnancy in the mediterranean region: A systematic review. *Eur. J. Clin. Nutr.* **2016**, *70*, 979–986. [CrossRef] [PubMed]
25. Perez-Lopez, F.R.; Fernandez-Alonso, A.M.; Ferrando-Marco, P.; Gonzalez-Salmeron, M.D.; Dionis-Sanchez, E.C.; Fiol-Ruiz, G.; Chedraui, P. First trimester serum 25-hydroxyvitamin d status and factors related to lower levels in gravids living in the spanish mediterranean coast. *Reprod. Sci.* **2011**, *18*, 730–736. [CrossRef] [PubMed]

26. Perez-Ferre, N.; Torrejon, M.J.; Fuentes, M.; Fernandez, M.D.; Ramos, A.; Bordiu, E.; del Valle, L.; Rubio, M.A.; Bedia, A.R.; Montanez, C.; et al. Association of low serum 25-hydroxyvitamin d levels in pregnancy with glucose homeostasis and obstetric and newborn outcomes. *Endocr. Pract. Off. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol.* **2012**, *18*, 676–684. [CrossRef] [PubMed]
27. Fernandez-Alonso, A.M.; Dionis-Sanchez, E.C.; Chedraui, P.; Gonzalez-Salmeron, M.D.; Perez-Lopez, F.R.; The Spanish Vitamin D and Women's Health Research Group. First-trimester maternal serum 25-hydroxyvitamin d(3) status and pregnancy outcome. *Int. J. Gynaecol. Obstet. Off. Organ Int. Fed. Gynaecol. Obstet.* **2012**, *116*, 6–9.
28. Fernandez-Alonso, A.M.; Valdera-Simbron, C.J.; Fiol-Ruiz, G.; Rodriguez-Sanchez, F.; Chedraui, P.; Perez-Lopez, F.R. First trimester serum levels of 25-hydroxyvitamin d, free beta-human chorionic gonadotropin, and pregnancy-associated plasma protein a in spanish women. *Gynecol. Endocrinol. Off. J. Int. Soc. Gynecol. Endocrinol.* **2011**, *27*, 1061–1064. [CrossRef] [PubMed]
29. Vandevijvere, S.; Amsalkhir, S.; Van Oyen, H.; Moreno-Reyes, R. High prevalence of vitamin d deficiency in pregnant women: A national cross-sectional survey. *PLoS ONE* **2012**, *7*, e43868. [CrossRef] [PubMed]
30. Van der Meer, I.M.; Karamali, N.S.; Boeke, A.J.; Lips, P.; Middelkoop, B.J.; Verhoeven, I.; Wuister, J.D. High prevalence of vitamin d deficiency in pregnant non-western women in The Hague, The Netherlands. *Am. J. Clin. Nutr.* **2006**, *84*, 350–353. [PubMed]
31. Viljakainen, H.T.; Saarnio, E.; Hytinantti, T.; Miettinen, M.; Surcel, H.; Makitie, O.; Andersson, S.; Laitinen, K.; Lamberg-Allardt, C. Maternal vitamin d status determines bone variables in the newborn. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 1749–1757. [CrossRef] [PubMed]
32. Bodnar, L.M.; Simhan, H.N.; Powers, R.W.; Frank, M.P.; Cooperstein, E.; Roberts, J.M. High prevalence of vitamin d insufficiency in black and white pregnant women residing in the northern united states and their neonates. *J. Nutr.* **2007**, *137*, 447–452. [PubMed]
33. Libon, F.; Cavalier, E.; Nikkels, A.F. Skin color is relevant to vitamin d synthesis. *Dermatology* **2013**, *227*, 250–254. [CrossRef] [PubMed]
34. Markestad, T.; Elzouki, A.; Legnain, M.; Ulstein, M.; Aksnes, L. Serum concentrations of vitamin d metabolites in maternal and umbilical cord blood of libyan and norwegian women. *Hum. Nutr. Clin. Nutr.* **1984**, *38*, 55–62. [PubMed]
35. Prentice, A. Vitamin d deficiency: A global perspective. *Nutr. Rev.* **2008**, *66*, S153–S164. [CrossRef] [PubMed]
36. Haddow, J.E.; Neveux, L.M.; Palomaki, G.E.; Lambert-Messerlian, G.; Canick, J.A.; Grenache, D.G.; Lu, J. The relationship between pth and 25-hydroxy vitamin d early in pregnancy. *Clin. Endocrinol.* **2011**, *75*, 309–314. [CrossRef] [PubMed]
37. Weishaar, T.; Rajan, S.; Keller, B. Probability of vitamin d deficiency by body weight and race/ethnicity. *J. Am. Board Fam. Med. JABFM* **2016**, *29*, 226–232. [CrossRef] [PubMed]
38. Brembeck, P.; Winkvist, A.; Olausson, H. Determinants of vitamin d status in pregnant fair-skinned women in Sweden. *Br. J. Nutr.* **2013**, *110*, 856–864. [CrossRef] [PubMed]
39. Lundqvist, A.; Sandstrom, H.; Stenlund, H.; Johansson, I.; Hultdin, J. Vitamin d status during pregnancy: A longitudinal study in swedish women from early pregnancy to seven months postpartum. *PLoS ONE* **2016**, *11*, e0150385. [CrossRef] [PubMed]
40. Eggemoen, A.R.; Falk, R.S.; Knutsen, K.V.; Lagerlov, P.; Sletner, L.; Birkeland, K.I.; Jenum, A.K. Vitamin d deficiency and supplementation in pregnancy in a multiethnic population-based cohort. *BMC Pregnancy Childbirth* **2016**, *16*, 7. [CrossRef] [PubMed]
41. Palacios, C.; De-Regil, L.M.; Lombardo, L.K.; Pena-Rosas, J.P. Vitamin d supplementation during pregnancy: Updated meta-analysis on maternal outcomes. *J. Steroid Biochem. Mol. Biol.* **2016**, *164*, 148–155. [CrossRef] [PubMed]
42. De-Regil, L.M.; Palacios, C.; Lombardo, L.K.; Pena-Rosas, J.P. Vitamin d supplementation for women during pregnancy. *Cochrane Database Syst. Rev.* **2016**, *1*, CD008873.
43. Freisling, H.; Fahey, M.T.; Moskal, A.; Ocke, M.C.; Ferrari, P.; Jenab, M.; Norat, T.; Naska, A.; Welch, A.A.; Navarro, C.; et al. Region-specific nutrient intake patterns exhibit a geographical gradient within and between european countries. *J. Nutr.* **2010**, *140*, 1280–1286. [CrossRef] [PubMed]

44. Bjorn Jensen, C.; Thorne-Lyman, A.L.; Vadgard Hansen, L.; Strom, M.; Odgaard Nielsen, N.; Cohen, A.; Olsen, S.F. Development and validation of a vitamin d status prediction model in danish pregnant women: A study of the danish national birth cohort. *PLoS ONE* **2013**, *8*, e53059.
45. Rodriguez, A.; Santa Marina, L.; Jimenez, A.M.; Esplugues, A.; Ballester, F.; Espada, M.; Sunyer, J.; Morales, E. Vitamin d status in pregnancy and determinants in a southern european cohort study. *Paediatr. Perinat. Epidemiol.* **2016**, *30*, 217–228. [CrossRef] [PubMed]

5.3 Publication III

Krieger JP, Cabaset S, Canonica C, Christoffel L, Richard A, Schröder T, Lipp von Wattenwyl B, Rohrmann S, **Quack Loetscher KC** (2018)

Prevalence and determinants of vitamin D deficiency in the third trimester of pregnancy: a multicentric study in Switzerland.

Accepted in British Journal of Nutrition, 2017

Full title: Prevalence and determinants of vitamin D deficiency in the third trimester of pregnancy: a multicenter study in Switzerland

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Running title: Vitamin D in near-term women and cord blood

Keywords (7) :

25-hydroxy-vitamin D, hypovitaminosis, cord blood, vitamin supplementation, neonates.

Abstract:

Vitamin D deficiency during pregnancy is associated with negative health consequences for mothers and their infants. Data on the vitamin D status of pregnant women in Switzerland are scarce. A three-center study was conducted in the obstetric departments of Zurich, Bellinzona and Samedan (Switzerland) to investigate the prevalence and determinants of vitamin D deficiency (serum 25(OH)D < 50 nmol/L) in 3rd-trimester pregnant women living in Switzerland (n=305), and the correlation between 25(OH)D in pregnant women and their offspring at birth (n=278). Demographic and questionnaire data were used to explore the determinants of vitamin D deficiency. Median concentration of serum 25(OH)D in the 3rd trimester of pregnancy was 46.0 nmol/L (1st-3rd quartiles: 30.5-68.5), representing a 53.4% prevalence of vitamin D deficiency. 25(OH)D levels in the umbilcal cord blood (median: 50.0 nmol/L [1st-3rd quartiles: 31.0-76.6]) strongly correlated mothers' serum 25(OH)D (Spearman's correlation rho=0.79, p<0.0001). Multivariable logistic regression analysis showed that significant determinants of vitamin D deficiency in pregnant women were center of study, country of origin, season of delivery, and vitamin D supplement intake. Near-term BMI, skin colour, use of sunscreen and mothers' education, although each not individually significant, collectively improved the ability of the model to explain vitamin D status. Low vitamin D levels were common in this sample of pregnant women and their newborns' cord blood. Vitamin D supplement intake was the most actionable determinant of vitamin D status, suggesting that vitamin D supplementation during pregnancy should receive more attention in clinical practice.

Introduction:

Vitamin D deficiency has been demonstrated in various populations and is therefore considered a widespread health issue [1,2]. The discovery that vitamin D is required for normal human growth and development has brought increasing attention to the potential health consequences of vitamin D deficiency during pregnancy [3].

Numerous studies have investigated the risks in mothers associated with low vitamin D levels during pregnancy (see [4] for review). In summary, there is evidence to suggest a link between low vitamin D status during pregnancy and preeclampsia, gestational diabetes, and preterm delivery [4-6]. Moreover, 25-hydroxyvitamin D (25(OH)D) concentrations in cord blood strongly correlate with maternal concentrations [7-10]: thus, vitamin D deficiency in pregnant women may also negatively impact fetal development. Some evidence indicates that babies' body size, bone mineralization, or risk of acute lower respiratory infections may be affected by low vitamin D status during pregnancy [3,4].

While these associations require further confirmation, they raise the question of vitamin D sufficiency in pregnant women. Studies reporting the prevalence of vitamin D deficiency in pregnant women are not easily comparable because cut-off values for vitamin D deficiency and insufficiency in pregnant women were not uniformly defined ([11-14], for example). Nevertheless, in all populations studied, the reported prevalence of vitamin D deficiency was consistently high at or near term [15,16]. These data, however, are not available for women in late pregnancy living in Switzerland. In addition, there are currently no data assessing the vitamin D status of neonates in Switzerland, and no 25(OH)D cut-off values are currently defined for newborns.

Reported determinants of vitamin D status in pregnant women are partly identical to those of the general population, including skin pigmentation, adiposity status, latitude of residence, dietary intake, use of vitamin supplements, wearing of skin-covering clothes or sunscreen use [7,12,17-19]. These determinants, however, appear to be country- and culturally-specific [1,15]. For example, classic determinants of vitamin D status fail to fully explain the high prevalence of vitamin D inadequacy in pregnant women of the Mediterranean region [20]. Interestingly, Switzerland is characterized by several factors that are indirectly linked with known vitamin D determinants: a unique blend of cultural influences, a large foreign population, a high diversity of meteorological conditions (for example Alpine and Mediteranean), and a large variability of altitude of residence. Consequently, there are reasons to believe that the determinants of vitamin D status in Swiss pregnant women may differ from other populations.

Moreover, in studies looking at vitamin D deficiency, many determinants are often reported, such as latitude of residence, season or physical activity [21,22]. This raises the question whether they are all equally important and whether there may be redundant factors. The comparative analysis of several regression models could help strengthen the identification of determinants [23] and potentially lead to simple prediction models of great use in routine clinical practice [24].

In this study, we measured serum 25(OH)D levels in women living in Switzerland during the 3rd trimester of pregnancy and in the cord blood of their offspring at birth. To better capture the potential heterogeneity of the Swiss population, we conducted the study in three centers representing regions of different cultural and meteorological influences. These data, together with demographic and questionnaire data, allowed us to 1) determine the prevalence of vitamin D deficiency in pregnant women and their neonates, 2) identify the significant determinants of vitamin D deficiency in pregnant women, and 3) test the relative importance of the selected determinants of vitamin D deficiency using a comparative analysis of several logistic regression models. Altogether, our data contribute to increased knowledge regarding maternal and neonatal vitamin deficiency in the Swiss population.

Methods:

Study population

The multicenter study was conducted between August 2014 and June 2016 at the obstetrics departments of the Zurich University Hospital, the Regional Hospital of Bellinzona and the Hospital of Oberengadin in Samedan. Women were conveniently recruited in the three centers during their last routine examination, *i.e.* within days prior to delivery (pregnancy weeks 36-42). Twin pregnancy, HIV, history of parathyroid, renal or liver disease, chronic malabsorption syndromes or granuloma-forming disorders, age below 18 years and known or suspected drug or alcohol abuse were used as exclusion criteria.

The study was not designed to be representative of the whole Swiss population but the choice of the three centers takes into account the cultural, socio-demographic and meteorological heterogeneity of Switzerland. Center regional characteristics are recapitulated in Figure 1. Briefly, Zurich is a densely-populated urban area with mild climate. The Bellinzona region is a less densely-populated area, with high temperatures and sunshine time, and belongs to the Italian-speaking region of Switzerland. The Samedan center is located in a rural region characterized by high altitude and low annual average temperatures. Meteorological data were supplied by IDAWEB (Swiss Federal Office of Meteorology and Climatology MeteoSwiss):

monthly total sunshine duration in hours and monthly mean of air temperature 2 meters above the ground were respectively summed and averaged over the study period (August 2014 to June 2016). Meteorological data were not available for Bellinzona and replaced by the neighbouring weather station of Locarno-Monti (20 km away). Demographic data are based on the Federal Statistical Office Swiss Atlas Data [25] and reflect the cantonal mean.

Justification of sample size

A true sample size calculation for our main analyses, the multivariable logistic regressions, required information that was unavailable in practice, such as the coefficients of determination between covariates. We therefore followed the indication of Agresti [26] to include a minimum of 10 particpants per covariate (305 participants for a maximum of 15 covariates in model 1).

Ethical approval

This study was conducted according to the guidelines set forth in the Declaration of Helsinki and all procedures involving human subjects were approved by the Zurich cantonal ethics committee (KEK-ZH-0213). Written informed consent was obtained from all subjects.

Blood collection

A 10 mL blood sample was taken from pregnant women during the last routine examination before delivery. Umbilical cord blood was taken post partum from the umbilical vein after clamping.

Measurements of serum 25(OH)D

Vitamin D status was evaluated by measuring the concentration of serum 25(OH)D, the main circulating metabolite of vitamin D, thus reflecting both dietary intake and endogenous production. Blood samples from mothers and umbilical cord were analyzed locally: the Institute of Clinical Chemistry of the Zurich University Hospital and Viollier AG (Arlesheim, Switzerland) for the Samedan Hospital used a vitamin D total-analysis Roche Cobas electrochemiluminescence immunoassay (Roche Diagnostics). The method has a detection range of 3.0–70.0 ng/mL for 25(OH)D and a variation coefficient of 2.2%–6.8%. The Department of Laboratory Medicine of Bellinzona Cantonal Hospital used an Agilent LC-MS/MS 6490 equipped with an 1290 LC series with the Chromsystems IVD kits and an automatic sample preparation (MassStar, Hamilton). The interassay variation coefficient was 6.5%-9.3%.

Definition of vitamin D deficiency

We chose a cut-off value of 50 nmol/L, as proposed by several authorities, including the Endocrine Society [27], the International Osteoporosis Foundation [28], or the Canadian

Osteoporosis Society [29]. Therefore, vitamin D deficiency was defined as serum level < 50 nmol/L and sufficiency as ≥ 50 nmol/L. Because no 25(OH)D cut-off values are currently defined for neonates (or cord blood), neonates were not referred to as sufficient or deficient.

Potential determinants of vitamin D status in pregnant women

Based on a questionnaire and data collected by physicians, the following variables were used as potential determinants: study center (Zurich vs. Bellinzona vs. Samedan), age, week of pregnancy, nulliparity (yes vs. no), first pregnancy (yes vs. no), self-reported BMI before pregnancy, measured BMI at near term, body weight gained during pregnancy, skin colour (light vs. dark), country of origin (in 5 groups), education level achieved by the mother, education level achieved by the partner (less than compulsory education vs. compulsory education vs. secondary education vs. tertiary education), smoking status (never vs. former vs. current), season (winter [December 21st - March 20th] vs. spring [March 21st - June 20th] vs. summer [June 21st - September 20th] vs. fall [September 21st - December 20th]), average number of days per week spent at least one hour outdoor between 10 am and 4pm in the past 6 months, frequency of sunscreen use when exposed to the sun in the summer (never vs. sometimes vs. always), consumption of fish (herring, salmon, mackerel, sardine or tuna) at least once a week (yes vs. no) and intake of vitamin D-containing supplements (yes vs. no).

The countries of origin were grouped into 5 categories based on the local population and the regions defined by the World Bank, as previously reported [19]: 1) Switzerland and Germany, 2) Northern America, Northern Europe, Central Asia and New-Zealand, 3) Southern Europe, Australia and Latin America, 4) South and East Asia and Pacific, and 5) Africa and Middle East.

To assess skin colour, we used a five-level scale [19] adapted from Fitzpatrick's classification method [30]. Briefly, the participants evaluated their phototype by choosing among five pictures the one that best represents their skin colour and describing how their untanned skin reacts to sun exposure (if exposed in the early summer at noon for 45 to 60 min). Physicians also evaluated the participants' skin colour. When the classification of the participant and the physician disagreed, the rounded arithmetic mean was taken. To account for the small amount of women in groups IV and V, the skin colour variable was then dichotomized into light skin colour (Fitzpatrick levels I to III) and dark skin colour (Fitzpatrick levels IV and V).

Descriptive analyses

All analyses and graphs were conducted using R (version 3.3.2 for Mac). Boxplots represent the median, 1st and 3rd quartiles of the complete cases. Prevalence of vitamin D deficiency between centers were compared using Kruskal-Wallis test followed by pairwise comparisons

158 using Tukey and Kramer-Nemenyi test with Tukey-Dist approximation for independent
159 samples. The correlation between serum 25(OH)D levels of pregnant women and the cord
160 blood of their neonates was determined using Spearman's correlation coefficient rho. P-values
161 ≤ 0.05 were considered significant.
162 *Logistic regression analyses of the determinants of vitamin D deficiency*
163 To increase the number of cases available for logistic regression, we assumed that data were
164 missing at random and performed multiple imputation with chained equations (m = 25, mice
165 package version 2.30 for R [31]). We estimated univariable associations of 25(OH)D
166 deficiency with potential determinants using logistic regressions, with the following variables:
167 study center, age, week of pregnancy, nulliparity, first pregnancy, BMI before pregnancy,
168 BMI near term, body weight gained during pregnancy, skin colour, country of origin,
169 education level achieved by the mother, education level achieved by the partner, smoking
170 status, season, days spent in the sun, use of sunscreen, fish consumption, intake of vitamin D-
171 containing supplements. In addition, we performed multivariable logistic regressions using all
172 potential determinants except variables showing high collinearity (Model 1). Collinearity was
173 defined as a Pearson's correlation coefficient above |0.6| between continuous variables and a
174 Cramér's V above 0.6 between categorical variables. Correlation coefficients and Cramér's V
175 were calculated on complete cases.
176 Two supplementary logistic regression models (models 2 and 3) were determined using the
177 following criteria: model 2 included the significant determinants of model 1 as well as the
178 variables signifcantly associated with vitamin D deficiency in an univariable model, whereas
179 model 3 included only the significant determinants of model 1. For all models, the measure of
180 association was the odd ratio (OR) and its corresponding 95% confidence interval (95% CI).
181 Reported regression coefficients are those obtained after combination with Rubin's rules (27).
182 *Comparative analysis of three logistic regression models of vitamin D deficiency*
183 For the three regression models, the Akaike Information Criterion (AIC) and the area under
184 the curve of the receiver operating characteristics (c-statistic) were calculated on complete
185 cases common to all models (n=219). In addition, observed vs. predicted probability of
186 vitamin D deficiency were plotted after recursive discretization of the data between upper and
187 lower halves and averaging of both the observed and predicted probabilities within each bin.
188 Circle area is proportional to the number of observations within a bin.
189
190 **Results:**
191 *General characteristics of the studied population*

305 women were included in the study (Table 1): 66.6% of the women were studied in Zurich (n=203), while the remainder was split between Bellinzona and Samedan (16.7%, n=51 in both centers). Overall, women were on average 32.9 (standard deviation [SD] 5.2) years old and 35.7% of them originated from Switzerland or Germany. Median week of pregnancy was 38 weeks, a time during which women had gained an average of 13.6 (SD 5.7) kg of body weight. A large majority of the women had secondary or tertiary education (69.8 %), did not smoke during pregnancy (90.5 %), ate fish at least once a week (60.3 %) and consumed vitamin D supplements (70.8 %). 86.9 % were fair-skinned, regularly spent time in the sun (median of 5 days per week during which at least one hour was spent in the sun), and used sunscreen in the summer (82.3 % at least sometimes).

Prevalence of vitamin D deficiency in pregnant women

Overall, prevalence of vitamin D deficiency was 53.4 % in the study sample. Median serum 25(OH)D concentration was 46.0 nmol/L (1^{st}-3^{rd} quartiles: 30.5-68.5) and was signficantly higher in Bellinzona than in Zurich ($p < 0.005$) and Samedan ($p < 0.0005$).

25(OH)D levels in the umbilical cord blood of neonates

In the cord blood of the neonates (n=283), median serum 25(OH)D level was 50.0 nmol/L (1^{st}-3^{rd} quartiles: 31.0-76.6), resulting in 49.8 % of the neonates having a 25(OH)D concentration below 50 nmol/L. A strong correlation was observed between serum 25(OH)D levels of the mothers and their neonates (Spearman's correlation rho=0.79, $p<0.0001$, Figure 2E).

Determinants of vitamin D deficiency in pregnant women

Univariable logistic regression showed that significant determinants of vitamin D deficiency were center of study, near-term BMI, country of origin, education of the mother and her partner, season, and use of sunscreen (Table 2). We further examined potential determinants of vitamin D deficiency in a multivariable logistic regression. On the basis of a correlation analysis, the following pairs of variables were considered to be collinear: nulliparity / first pregnancy (Cramér's V = 0.85), education of the mother / education of the partner (Cramér's V = 0.61), and BMI before pregnancy / near-term BMI (Pearson's correlation = 0.90): hence, nulliparity, education of the partner and BMI before pregnancy were left out of the first multivariable model (model 1). Center of study, country of origin, and season remained significant determinants of vitamin D deficiency in this model (Table 2). In addition, the use of vitamin D supplements became strongly associated with a lower risk of vitamin D deficiency. Conversely, near-term BMI, education of the mother, and use of sunscreen failed to reach statistical significance (Table 2). Surprisingly, after multivariable adjustment, a dark

skin colour was moderately associated with a decreased risk of vitamin D deficiency (Table 2). The 25(OH)D values accross levels of the significant determinants are shown in Figure 2 A-D. We used center, near-term BMI, skin colour, country of origin, season, education of the mother, use of sunscreen, use of vitamin D supplements in a second model (Model 2) and center, country of origin, season and use of vitamin D supplements in a third model (model 3). In both cases, the odd ratios were only marginally different to those of the full multivariable model 1 (Table 2).

Comparative analysis of three logistic regression models of vitamin D deficiency in pregnant women

The AIC of models 2 and 3 were markedly smaller than the AIC of model 1, indicating that these 2 models are more parsimonious (Fig. 3B). The comparison of the c-statistics indicated that model 2 has a superior ability to explain vitamin D deficiency than model 3, and that this ability to explain is comparable to the full model 1 (Fig. 3C, Fig. 3D). In addition, the plots of observed vs. expected probability indicated a satisfactory calibration of all models, with model 2 most ressembling the full model 1. Together, these model diagnostics indicate that the fit of a logistic regression model containing the four significant determinants (center, country of origin, season and use of vitamin D supplements) can be markedly improved by the addition of further four variables (BMI near term, skin colour, education of the mother, use of sunscreen).

Discussion:

Vitamin D deficiency during pregnancy has been linked with several adverse health outcomes. Therefore, the fact that low serum levels were repeatedly found in pregnant women from different countries and at different stages of pregnancy is a matter of concern [3,15]. The prevalence and determinants of vitamin D inadequacy, however, seem to vary with the population studied [1,15]. Hence, to address the needs of the local population, it is therefore crucial to understand the country-specific determinants of vitamin D deficiency. To the best of our knowledge, our study is the first to investigate the prevalence and determinants of vitamin D deficiency in women living in Switzerland during the last trimester of pregnancy, and to measure 25(OH)D in the cord blood of their newborns. Beyond the local value of this information, our data may be of interest for other European countries because of Switzerland's specific blend of cultural and meteorological influences.

Data from our multicenter study indicate an overall prevalence of vitamin D deficiency of 53 % among women in the 3rd trimester of pregnancy in Switzerland. This overall prevalence is

somewhat comparable with the prevalence reported in neighbouring countries, such as Germany (77% [32]), Northern Italy (85% [33]), or France (41% [34]). More broadly, our results lie within the wide range of reported prevalence rates of vitamin D deficiency during pregnancy, whether the investigated populations are located in the Mediterranean region (22.7% to 90.3%, see [20] for review) or in the North of Europe (Belgium 45% [35], Finland 60% [36], Sweden 65% [17]).

Interestingly, in Switzerland, non-pregnant women showed a much lower all-year prevalence of vitamin D deficiency than the one reported here in pregnant women (35% [37]). Data directly comparing the vitamin D status of pregnant women with women of procreating age are scarce. Ritchie and colleagues [38] reported no significant differences in 25(OH)D measured in 14 women before pregnancy, during each trimester and during lactation. Some data, however, indicate that the 25(OH)D concentrations in early pregnancy do not differ from those of non pregnant women, but exhibit a significant decrease towards the end of pregnancy[39-41]. Several mechanisms could explain this decrease in 25(OH)D during pregnancy. First, 25(OH)D passes the placenta and the fetus is completely dependent on the maternal serum for vitamin D supply. The lower serum 25(OH)D of the mother could therefore reflect the placetal transfer to the growing fetus. Moreover, plasma PTH increases during pregnancy, thus potentially explaining the decrease in 25(OH)D during pregnancy [39]. Finally, certain authors hypothesized that the liver hydroxylation of vitamin D may be affected by pregnancy[40], because the modulation of different types of cytochrome P450 has been reported [42].

Furthermore, the prevalence of 25(OH)D concentrations below 50 nmol/L in the cord blood of newborns (49.8 %) is comparable to the prevalence of vitamin D deficiency in mothers (53.4 %). This strong correlation corroborates the numerous reports which show that concentrations of 25(OH)D in the cord blood at delivery correlate with those of the mothers [7-10], although the reported correlation coefficient does vary markedly between studies. Knowing the risk of disturbed fetal development, as well as diseases occuring later in life (diabetes, asthma) [4], the high prevalence of vitamin D deficiency in mothers and newborns is alarming.

An interesting feature of our study is the varying prevalence of vitamin D deficiency between the study centers (55% in Zürich, 33% in Bellinzona, 69% in Samedan). Hence, the specific study center (which is a proxy for the region in which women lived) was a strong determinant of vitamin D deficiency, *i.e.,* a variable found in all logistic regression models. Socio-demographic determinants are unlikely to explain the different prevalence of vitamin D

deficiency across centers, because Samedan and Bellinzona showed similar population characteristics (Table 1). Diversity of diets across centers may be a plausible cause, but our data on fish consumption, a major nutritional source of vitamin D, indicate similar consumption levels in Samedan and Bellinzona. Vitamin D intake, however, was not measured in our study, and this hypothesis cannot be fully discounted. Nevertheless, the most likely cause is the fact that differences in sunshine duration and outdoor temperature drive very diverse skin exposure time to UVB between the three centers (Figure 1B).

The intake of vitamin D-containing supplements (alone or as a multivitamin supplement) protected against vitamin D deficiency. The consumption of fish, however, was not a significant determinant of vitamin D deficiency. Here, we assessed fish consumption based on studies showing that fish and seafood are the main sources of dietary vitamin D in pregnant women and reflect the total dietary vitamin D intake [18]. Therefore, our findings are in accordance with studies showing that high vitamin D intake is mostly achieved by supplement intake rather than through diet [18]. These data further advocate for vitamin D supplementation during pregnancy. In support of this, several randomized control trials consistently showed that vitamin D supplements were effective to increase maternal 25(OH)D concentrations at term [6], umbilical cord venous and neonatal serum 25(OH)D as compared to a placebo [43-45].

Paradoxically, in our sample population, a high percentage of vitamin D supplement or multivitamin supplement intake (71%) did not prevent a high prevalence of vitamin D deficiency. This paradox may be explained by an inadequate or insufficient intake of vitamin D, despite the wide use of supplements. Indeed, in our study, we did not quantitatively evaluate vitamin D intake. Similarly, in a large sample of pregnant women from Denmark, only 30% of the population had an adequate vitamin D intake (defined by a daily intake of 10 µg/day – maximum reached after 30 weeks of pregnancy), whereas the majority of women (67.5%) took vitamin D supplements [18]. In addition, the type of vitamin D supplements reported was highly diverse (data not shown): brands, doses, single susbtance vs multivitamin mixes, countries of manufacture were the main factors of supplements heterogeneity. This indicates that, despite the existence of Swiss guidelines (600 IU vitamin D per day and 1500-2000 IU when deficiency is evident [46]), vitamin D intake during pregnancy remains partly inadequate. Further advice from medical practicionners may help women to chose adequate supplements and use them appropriately. However, even in the presence of a standardized vitamin D supplementation, the heterogeneity of 25(OH)D response to vitamin D supplementation has been documented [47-49] and includes genetic factors, BMI and baseline 25(OH)D levels. Therefore, this indicates that a successful vitamin D supplementation plan

would also require individualization on the basis of serum 25(OH)D measurement during pregnancy.

The comparative analysis of several logistic regression models allowed us to systematically test the relative importance of vitamin D determinants included in this study. Thus, we identified 4 core determinants of vitamin D deficiency (center of study, country of origin, season of delivery, intake of vitamin D supplements), as well as four secondary factors (*i.e.* factors not reaching significance individually but improving the goodness of fit of the model: education, near-term BMI, skin colour, use of sunscreen). The regression models, however, should not be considered as an attempt to find prediction formula for vitamin D deficiency in pregnant women in Switzerland. Indeed, the nature of our experimental design does not make these models suitable for prediction: first, only one dataset was available and used for the establishment of these models, thus, leaving no data available for external model validation. Second, the sample in this study was not designed to be representative of the Swiss population; consequently, the relevance of the models presented here are limited to our sample. In addition, due to the use of a multiple imputation strategy, the diagnostics of the models were limited. Eventually, we acknowledge that other potential determinants of vitamin D levels, such as nutritional intake, physical activity or genetic background, were not optimally investigated here and should be the objective of future studies.

In conclusion, our study was the first to our knowledge to address prevalence rates of vitamin D deficiency in late pregnancy in Switzerland. This study indicated that low vitamin D levels are common in this sample of pregnant women living in Switzerland, as well as in their neonates' cord blood. Using logistic regression analyses and model comparison, we identified the center of study, country of origin season of delivery and intake of vitamin D supplements as main determinants of vitamin D deficiency in pregnant women. As the intake of vitamin D supplement is the most likely actionable determinant identified in this study, it suggests that vitamin D supplementation during pregnancy should receive more attention in clinical practice.

Acknowledgements

We thank Dr. Sarah Haile (University of Zurich) for statistical support, Nina Pupikofer (National Institute for Cancer Epidemiology and Registration) for data entry, Dr. Kelly Turner for language check and editing suggestions, Dr. Marco Cantú (Biochemistry and Pharmacology Laboratory, Hospital of Bellinzona) and Dr. Massimo Locatelli (San Raffaele Hospital) for assistance in sample analysis and data interpretation, and all women who participated in this study. We thank the Swiss Federal Office of Meteorology and Climatology MeteoSwiss for providing summary weather data.

Financial support :

This work was supported by the Swiss National Science Foundation: NRP69 grant 4069-145194.

Conflicts of interest :

None

Author contributions

J.-P.K. analyzed data, and wrote the paper.

S.C. and A.R. analyzed data, and edited and reviewed the manuscript.

C.C., L.C., T.S., B.L.W. provided essential materials and conducted research (recruiting and sample collection).

S.R., K.Q.L. designed research, conducted research (recruiting and sample collection), edited and reviewed the manuscript and had primary responsability for final content.

All authors have read and approved the final manuscript.

References

1. Hilger J, Friedel A, Herr R, *et al*. (2014) A systematic review of vitamin D status in populations worldwide. *Br J Nutr* **111**, 23–45.

2. Palacios C, Gonzalez L. (2014) Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol* **144** Pt A, 138–45.

3. Dror DK, Allen LH. (2010) Vitamin D inadequacy in pregnancy: biology, outcomes, and interventions. *Nutr Rev* **68**, 465–77.

4. Moon RJ, Harvey NC, Cooper C. (2015) Endocrinology in pregnancy: Influence of maternal vitamin D status on obstetric outcomes and the fetal skeleton. *Eur J Endocrinol* **173**, 69–83.

5. Harvey NC, Holroyd C, Ntani G, *et al*. (2014) Vitamin D supplementation in pregnancy: a systematic review. *Health Technol Assess* **18**, 1–190.

6. De-Regil LM, Palacios C, Lombardo LK, *et al*. (2016) Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev* **CD008873**.

7. Bodnar LM, Catov JM, Roberts JM, *et al*. (2007) Prepregnancy obesity predicts poor vitamin D status in mothers and their neonates. *J Nutr* **137**, 2437–42.

8. Wegienka G, Kaur H, Sangha R, *et al*. (2016) Maternal-Cord Blood Vitamin D Correlations Vary by Maternal Levels. *J Pregnancy* **2016**, 7474192.

9. Markestad T, Aksnes L, Ulstein M, *et al*. (1984) 25-Hydroxyvitamin D and 1,25-dihydroxyvitamin D of D2 and D3 origin in maternal and umbilical cord serum after vitamin D2 supplementation in human pregnancy. *Am J Clin Nutr* **40**, 1057–63.

10. Maghbooli Z, Hossein-Nezhad A, Shafaei AR, *et al*. (2007) Vitamin D status in mothers and their newborns in Iran. BMC Pregnancy Childbirth **7**, 1.

11. Bassir M, Laborie S, Lapillonne A, *et al*. (2001) Vitamin D deficiency in Iranian mothers and their neonates: a pilot study. *Acta Paediatr* **90**, 577–9.

12. Bodnar LM, Simhan HN, Powers RW, *et al*. (2007) High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. *J Nutr* **137**, 447–52.

13. Holmes VA, Barnes MS, Alexander HD, *et al*. (2009) Vitamin D deficiency and insufficiency in pregnant women: a longitudinal study. *Br J Nutr* **102**, 876–81.

14. Molla AM, Badawi Al M, Hammoud MS, *et al*. (2005) Vitamin D status of mothers and their neonates in Kuwait. *Pediatr Int* **47**, 649–52.

15. Ponsonby A-L, Lucas RM, Lewis S, *et al*. (2010) Vitamin D status during Pregnancy and Aspects of Offspring Health. *Nutrients* **2**, 389–407.

16. Saraf R, Morton SMB, Camargo CAJ, *et al*. (2016) Global summary of maternal and newborn vitamin D status - a systematic review. *Matern Child Nutr* **12**, 647–68.

17. Brembeck P, Winkvist A, Olausson H. (2013) Determinants of vitamin D status in pregnant fair-skinned women in Sweden. *Br J Nutr* **110**, 856–64.

18. Jensen CB, Petersen SB, Granstrom C, *et al*. (2012) Sources and determinants of vitamin D intake in Danish pregnant women. *Nutrients* **4**, 259–72.

19. Richard A, Rohrmann S, Quack Lötscher KC. (2017) Prevalence of Vitamin D Deficiency and Its Associations with Skin Color in Pregnant Women in the First Trimester in a Sample from Switzerland. *Nutrients* **9**, 260.

20. Karras S, Paschou SA, Kandaraki E, *et al*. (2016) Hypovitaminosis D in pregnancy in the Mediterranean region: a systematic review. *Eur J Clin Nutr* **70**, 979–86.

21. Rodriguez A, Santa Marina L, Jimenez AM, *et al*. (2016) Vitamin D Status in Pregnancy and Determinants in a Southern European Cohort Study. *Paediatr Perinat Epidemiol* **30**, 217–28.

22. Dovnik A, Mujezinović F, Treiber M, *et al*. (2017) Determinants of maternal vitamin D concentrations in Slovenia : A prospective observational study. *Wien Klin Wochenschr* **129**, 21–8.

23. Zgaga L, Agakov F, Theodoratou E, *et al*. (2013) Model Selection Approach Suggests Causal Association between 25-Hydroxyvitamin D and Colorectal Cancer. *PLoS ONE* **8**, e63475.

24. Sohl E, Heymans MW, de Jongh RT, *et al*. (2014) Prediction of vitamin D deficiency by simple patient characteristics. *Am J Clin Nutr* **99**, 1089–95.

25. Federal Statistical Office - Statistical Atlas of Switzerland https://www.atlas.bfs.admin.ch (accessed October 2017)

26. Agresti A. (2007) *An Introduction to Categorical Data Analysis.* 2nd ed. John Wiley & Sons.

27. Holick MF, Binkley NC, Bischoff-Ferrari HA, *et al*. (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* **96**, 1911–30.

28. Dawson-Hughes B, Mithal A, Bonjour J-P, *et al*. (2010) IOF position statement: vitamin D recommendations for older adults. *Osteoporos Int* **21**, 1151–4.

29. Hanley DA, Cranney A, Jones G, *et al.* (2010) Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. *CMAJ* **182**, E610–8.

30. Fitzpatrick TB. (1988) The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol* **124**, 869–71.

31. Buuren SV, Groothuis-Oudshoorn K. (2011) mice: Multivariate Imputation by Chained Equations in R. *J Stat Software* **45**, 1-67**.**

32. Wuertz C, Gilbert P, Baier W, *et al*. (2013) Cross-sectional study of factors that influence the 25-hydroxyvitamin D status in pregnant women and in cord blood in

Germany. *Br J Nutr* **110**, 1895–902.

33. Cadario F, Savastio S, Magnani C, *et al*. (2015) High Prevalence of Vitamin D Deficiency in Native versus Migrant Mothers and Newborns in the North of Italy: A Call to Act with a Stronger Prevention Program. *PLoS ONE 2015* **10**, e0129586.

34. Ceccaldi P-F, Pejoan H, Breau N, *et al*. (2017) French prenatal Vitamin D recommended supplementation: Enough or not? *J Gynecol Obstet Biol Reprod* **46**, 35-41.

35. Vandevijvere S, Amsalkhir S, Van Oyen H, *et al*. (2012) High prevalence of vitamin D deficiency in pregnant women: a national cross-sectional survey. *PLoS ONE* **7**, e43868.

36. Viljakainen HT, Saarnio E, Hytinantti T, *et al*. (2010) Maternal vitamin D status determines bone variables in the newborn. *J Clin Endocrinol Metab* **95**, 1749–57.

37. Guessous I, Dudler V, Glatz N, *et al*. (2012) Vitamin D levels and associated factors: a population-based study in Switzerland. *Swiss Med Wkly* **142**, w13719.

38. Ritchie LD, Fung EB, Halloran BP, *et al.* (1998) A longitudinal study of calcium homeostasis during human pregnancy and lactation and after resumption of menses. *Am J Clin Nutr* **67**, 693–701.

39. Ardawi MS, Nasrat HA, BA'Aqueel HS. (1997) Calcium-regulating hormones and parathyroid hormone-related peptide in normal human pregnancy and postpartum: a longitudinal study. *Eur J Endocrinol* **137**, 402–9.

40. Salle BL, Delvin EE, Lapillonne A, *et al*. (2000) Perinatal metabolism of vitamin D. *Am J Clin Nutr* **71**,1317S–24S.

41. Zhang JY, Lucey AJ, Horgan R, *et al*. (2014) Impact of pregnancy on vitamin D status: a longitudinal study. *Br J Nutr* **112**, 1081–7.

42. Anderson GD. (2005) Pregnancy-Induced Changes in Pharmacokinetics. *Clin Pharmacokinet* **44**, 989–1008.

43. Hollis BW, Johnson D, Hulsey TC, *et al*. (2011) Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. *J Bone Miner Res* **26**, 2341–57.

44. Wagner CL, McNeil RB, Johnson DD, *et al.* (2013) Health characteristics and outcomes of two randomized vitamin D supplementation trials during pregnancy: a combined analysis. *J Steroid Biochem Mol Biol* **136**, 313–20.

45. Dawodu A, Saadi HF, Bekdache G, *et al*. (2013) Randomized controlled trial (RCT) of vitamin D supplementation in pregnancy in a population with endemic vitamin D deficiency. *J Clin Endocrinol Metab* **98,** 2337–46.

46. Quack Lötscher KC, l'Allemand D, Bischoff-Ferrari HA, *et al*. (2012) *Vitamin D deficiency: Evidence, safety, and recommendations for the Swiss population*. Federal Office of Publich Health, Switzerland.

47. Fu L, Yun F, Oczak M, *et al*. (2009) Common genetic variants of the vitamin D binding protein (DBP) predict differences in response of serum 25-hydroxyvitamin D [25(OH)D] to vitamin D supplementation. *Clin Biochem* **42**, 1174–7.

48. Didriksen A, Grimnes G, Hutchinson MS, *et al*. (2013) The serum 25-hydroxyvitamin D response to vitamin D supplementation is related to genetic factors, BMI, and baseline levels. *Eur J Endocrinol***169**, 559–67.

49. Moon RJ, Harvey NC, Cooper C, *et al*. (2016) Determinants of the Maternal 25-Hydroxyvitamin D Response to Vitamin D Supplementation During Pregnancy. *J Clin Endocrinol Metab* **101**, 5012–20.

	Overall		Zurich		Bellinzona		Samedan	
		Missing		Missing		Missing		Missing
n (% of total women included)	305 (100)	0	203 (66.6)	0	51 (16.7)	0	51 (16.7)	0
Mothers, 25(OH)D < 50 nmol/L, n (%)	163 (53.4)	0	111 (54.7)	0	17 (33.3)	0	35 (68.6)	0
Mothers, 25(OH)D nmol/L, median (Q1, Q3)	46.0 (30.5-60.8)	0	44.8 (29.9-69.4)	0	63.8 (41.3-90.4)	0	41.0 (28.0-52.5)	0
Babies, 25(OH)D < 50 nmol/L, n (%)	141 (49.8)	22	83 (40.9)	17	29 (56.9)	5	29 (56.9)	0
Babies, 25(OH)D nmol/L, median (Q1, Q3)	50.0 (31.0-76.6)	22	59.4 (32.0-82.9)	17	40.4 (23.6-55.4)	5	46.0 (30.5-62.0)	0
Age, mean (SD)	32.9 (5.2)	0	33.6 (5.1)	0	31.2 (5.1)	0	32 (5.6)	0
Week of pregnancy, median (Q1, Q3)	38 (38-39)	1	38 (38-38)	0	40 (39-40)	0	39 (37-40)	1
Nulliparity, n (%)	120 (39.3)	1	60 (29.6)	0	23 (45.1)	1	37 (72.6)	0
First pregnancy, n (%)	102 (33.4)	1	51 (25.1)	0	19 (37.3)	0	32 (62.8)	1
BMI before pregnancy, median (Q1, Q3)	22.9 (20.7-25.4)	40	23.2 (21.2-25.7)	16	23.1 (21.2-25.8)	24	21.5 (20.0-23.8)	0
BMI near term, median (Q1, Q3)	28.0 (25.4-30.8)	11	27.9 (25.6-30.9)	2	28.4 (25.6-30.7)	9	28.0 (24.5-30.1)	0
BW gain during pregnancy, mean (SD)	13.6 (5.7)	42	13.4 (5.7)	19	13.2 (4.7)	23	14.4 (6.3)	0
Skin colour, n (%)		6		1		5		0
Light	265 (86.9)		173 (85.2)		44 (86.3)		48 (94.1)	
Dark	34 (11.2)		29 (14.3)		2 (3.9)		3 (5.9)	
Country of origin, n (%)		4		2		2		0
Group 1	109 (35.7)		67 (33.0)		21 (41.2)		21 (41.2)	
Group 2	74 (24.3)		62 (30.5)		7 (13.7)		5 (9.8)	
Group 3	72 (23.6)		30 (14.8)		18 (35.3)		24 (47.1)	
Group 4	21 (6.9)		18 (8.9)		2 (3.9)		1 (2.0)	
Group 5	25 (8.2)		24 (11.8)		1 (2.0)		0 (0)	
Education, n (%)		30		19		5		6
Less than compulsory	12 (3.9)		9 (4.4)		0 (0)		3 (5.9)	
Compulsory	50 (16.4)		30 (14.8)		7 (13.7)		13 (25.5)	
Secondary	111 (36.4)		62 (30.5)		27 (52.9)		22 (43.1)	
Tertiary	102 (33.4)		83 (40.9)		12 (23.5)		7 (13.7)	
Education of the partner, n (%)		40		27		7		6
Less than compulsory	15 (4.9)		11 (5.4)		1 (2.0)		3 (5.9)	
Compulsory	37 (12.1)		18 (8.9)		6 (11.8)		13 (25.5)	
Secondary	112 (36.7)		62 (30.5)		26 (51.0)		24 (47.1)	
Tertiary	101 (33.1)		85 (41.9)		11 (21.6)		5 (9.8)	
Smoking status, n (%)		2		1		1		0
Never	187 (61.3)		122 (60.1)		32 (62.8)		33 (64.7)	
Ever	89 (29.2)		61 (30.1)		14 (27.5)		14 (27.5)	
Current	27 (8.9)		19 (9.4)		4 (7.8)		4 (7.8)	
Season, n (%)		0		0		0		0
Winter	78 (25.6)		65 (32.0)		11 (21.6)		2 (3.9)	
Spring	107 (35.1)		79 (38.9)		10 (19.6)		18 (35.3)	
Summer	39 (12.8)		20 (9.9)		11 (21.6)		8 (15.7)	
Fall	81 (26.6)		39 (19.21)		19 (37.3)		23 (45.1)	
Days per week spent at least 1 h outdoor in the past 6 months, median (Q1, Q3)	5 (2-7)	15	4 (2-7)	5	6 (3-7)	5	5 (2-7)	5
Using sun protection in summer, n (%)		3		1		1		1
Never	51 (16.7)		42 (20.7)		7 (13.7)		2 (3.9)	
Sometimes	130 (42.6)		81 (39.9)		25 (49.0)		24 (47.1)	
Always	121 (39.7)		79 (38.9)		18 (35.3)		24 (47.1)	
Fish consumption at least once a week, n (%)	184 (60.3)	6	109 (53.7)	2	37 (72.6)	2	38 (74.5)	2
Vitamin D supplement intake, n (%)	216 (70.8)	0	165 (81.3)	0	21 (41.2)	0	30 (58.8)	0

Table 1: General characteristics of the studied sample (n: number of individuals; Q1: first quartile; Q3: third quartile; SD: standard deviation; BW: body weight). Age is indicated in years, body weight gain in kg and BMI in kg/m^2. Skin colour was dichotomized in light (Fitzpatrick levels I to III) or dark colour (Fitzpatrick levels IV and V). Country groups are as follows: group 1) Switzerland and Germany, group 2) Northern America, Northern Europe, Central Asia and New-Zealand, group 3) Southern Europe, Australia and Latin America, group 4) South and East Asia and Pacific, and group 5) Africa and Middle East. Seasons were defined as follows : winter (December 21st - March 20th), spring (March 21st - June 20th), summer (June 21st - September 20th) and fall (September 21st - December 20th).

	Univariable models		Multivariable model 1		Multivariable model 2		Multivariable model 3	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Center								
Zurich	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Bellinzona	**0.41**	**0.22-0.79**	**0.29**	**0.11-0.78**	**0.36**	**0.16-0.80**	**0.40**	**0.19-0.86**
Samedan	1.81	0.94-3.49	**2.48**	**1.04-5.89**	**2.49**	**1.12-5.55**	**2.72**	**1.27-5.83**
Age	0.96	0.92-1.01	0.98	0.92-1.03	-	-	-	-
Week of pregnancy	0.93	0.76-1.13	1.12	0.85-1.49	-	-	-	-
Nulliparity	0.92	0.58-1.46	-	-	-	-	-	-
First pregnancy	0.78	0.48-1.25	0.75	0.41-1.37	-	-	-	-
BMI before pregnancy	1.05	1.00-1.11	-	-	-	-	-	-
BMI near term	**1.07**	**1.02-1.13**	1.04	0.98-1.11	1.05	0.99-1.11	-	-
BW gain during pregnancy	1.02	0.98-1.06	1.01	0.96-1.07	-	-	-	-
Skin colour								
Light	1	(ref)	1	(ref)	1	(ref)	-	-
Dark	1.27	0.61-2.60	0.39	0.14-1.12	0.41	0.15-1.12		
Country of origin								
Group 1	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Group 2	**2.73**	**1.48-5.03**	**2.33**	**1.15-4.73**	**2.40**	**1.21-4.75**	**2.99**	**1.56-5.74**
Group 3	**2.34**	**1.27-4.30**	**2.41**	**1.14-5.11**	**2.21**	**1.08-4.52**	**2.37**	**1.22-4.61**
Group 4	**4.32**	**1.55-12.03**	**7.27**	**1.92-27.55**	**7.81**	**2.16-28.23**	**5.63**	**1.85-17.15**
Group 5	**3.53**	**1.40-8.89**	**4.86**	**1.40-16.85**	**4.74**	**1.43-15.77**	**4.50**	**1.68-12.07**
Education								
Less than compulsory	1	(ref)	1	(ref)	1	(ref)	-	-
Compulsory	0.85	0.20-3.53	0.86	0.18-4.00	0.95	0.21-4.30	-	-
Secondary	0.46	0.12-1.75	0.67	0.16-2.85	0.66	0.16-2.77	-	-
Tertiary	**0.26**	**0.07-0.98**	0.39	0.09-1.69	0.39	0.10-1.58	-	-
Education of the partner								
Less than compulsory	1	(ref)	-	-	-	-	-	-
Compulsory	0.6	0.14-2.55	-	-	-	-	-	-
Secondary	0.38	0.10-1.40	-	-	-	-	-	-
Tertiary	**0.19**	**0.05-0.72**	-	-	-	-	-	-
Smoking status								
Never	1	(ref)	1	(ref)	-	-	-	-
Ever	0.84	0.50-1.39	0.92	0.50-1.69	-	-	-	-
Current	1.43	0.62-3.30	1.07	0.40-2.90	-	-	-	-
Season								
Winter	1	(ref)	1	(ref)	1	(ref)	1	(ref)
Spring	0.7	0.38-1.27	0.73	0.36-1.45	0.74	0.37-1.46	0.64	0.33-1.23
Summer	**0.41**	**0.19-0.91**	**0.33**	**0.13-0.86**	**0.33**	**0.13-0.84**	**0.31**	**0.13-0.75**
Fall	0.58	0.31-1.09	**0.45**	**0.20-0.98**	**0.40**	**0.19-0.86**	**0.40**	**0.19-0.83**
Days per week spent at least one hour outdoor in the past 6 months	0.97	0.89-1.07	0.97	0.87-1.08	-	-	-	-
Using sun protection in summer								
Never	1	(ref)	1	(ref)	1	(ref)	-	-
Sometimes	**0.38**	**0.19-0.77**	0.47	0.20-1.10	**0.44**	**0.20-1.00**	-	-
Always	**0.38**	**0.19-0.78**	0.61	0.25-1.50	0.57	0.24-1.32	-	-
Fish consumption at least once a weel	0.9	0.56-1.44	0.85	0.47-1.52	-	-	-	-
Vitamin D supplement intake	0.66	0.40-1.09	**0.42**	**0.22-0.80**	**0.42**	**0.22-0.80**	**0.43**	**0.23-0.79**

Table 2: Odds of vitamin D deficiency during pregnancy in the studied sample (n=305), results of univariable and multivariable logistic regressions. (BW: body weight; age was expressed in years, body weight gain in kg and BMI in kg/m^2). Multivariable model 1 was adjusted for: study center, age, week of pregnancy, first pregnancy, BMI near term, body weight gained during pregnancy, skin colour, country of origin, education level achieved by the mother, smoking status, season of delivery, days per week spent at least one hour outdoor in the past 6 months, use of sun protection in the summer, fish consumption, intake of vitamin D-containing supplements. Model 2 was adujsted for: study center, BMI near term, skin colour, country of origin, education level achieved by the mother, season of delivery, use of sun protection in the summer, intake of vitamin D-containing supplements. Model 3 was adjusted for: study center, country of origin, season of delivery, intake of vitamin D-containing supplements.

Figure legends

Figure 1: (A) Geographical distribution, **(B)** meteorological characteristics of the three study centers (source MeteoSwiss, [(1)] indicates that data were not available for Bellinzona and replaced by the neighbouring weather station of Locarno-Monti) and population density of the respective cantons (source Federal Statistical Office, Statistical Atlas of Switzerland [25]).

Figure 2: Serum 25(OH)D levels in pregnant women by **(A)** study center, **(B)** season of delivery, **(C)** country of origin, and **(D)** intake of vitamin D supplements. **(E)** Correlation between serum 25(OH)D concentration of pregnant women and the umbilical cord blood of their neonates (n=283).

Figure 3: (A) Variables included, **(B)** AIC, **(C)** receiver operating characteristic (ROC) curves and **(D)** observed vs. predicted value plots in all three logistic regression models. Model diagnostics were computed on complete cases common to the tree models (n=219).

6. Discussion and perspectives

Regarding nutritional counselling during pregnancy, we have only a few hard facts to offer to women. Due to the fact that many women are unaware of their pregnancy in the first weeks, counselling for folic acid, with its largest impact exerted pre-conceptionally, comes too late. Iron supplementation has gained clinical significance. But the art of supplementation, oral or intravenously, is still under debate. Particularly challenging is the question of oxidative stress of iron for both mother and child. Regarding vitamin D, it seems obvious that there is high prevalence of deficiency, but the dosage of vitamin D supplementation is not clear. Apart from reduction of premature delivery, other benefits of supplementation with vitamin D still need to be established.

Looking at the macronutrients, waves of different diet recommendations and fashions for the general population have shaped the counselling for pregnant women as well. From the present knowledge, it seems that only a little increase in calories at the right time during pregnancy is necessary, but the most important factor seems to be a balanced diet. Unfortunately, no social insurance statement in the basic insurance allows for reimbursement of nutrition counselling by specialized nutritionists for pregnant women.

Future studies should clarify which nutritional status is favourable for starting a pregnancy and which deficiencies need to be supplemented and in which form. The principals of balanced diet need to be explained by professionals. Equal importance should be given to the counselling about physical activity during pregnancy. This, reflecting the fact that energy balance can not only be regulated by food but also by exercise.

Counselling about nutrition and physical activity in pregnancy should reach women of different cultural backgrounds. As our first publication could show, not all groups need similar information. Therefore, further research targeting various ethical groups of pregnant women might bring new evidence in the field of nutrition, supplementation and overall life-style influence on pregnancy as well.

7. References

1. Shenassa, E.D., et al., *Gestational Weight Gain: Historical Evolution of a Contested Health Outcome.* Obstet Gynecol Surv, 2017. **72**(7): p. 445-453.
2. DACH, *Nährwertempfehlungen.* 2015.
3. Arabin, B. and A.A. Baschat, *Pregnancy: An Underutilized Window of Opportunity to Improve Long-term Maternal and Infant Health-An Appeal for Continuous Family Care and Interdisciplinary Communication.* Front Pediatr, 2017. **5**: p. 69.
4. Kapadia, M.Z., et al., *Weight Loss Instead of Weight Gain within the Guidelines in Obese Women during Pregnancy: A Systematic Review and Meta-Analyses of Maternal and Infant Outcomes.* PLoS One, 2015. **10**(7): p. e0132650.
5. Grooten, I.J., et al., *Weight loss in pregnancy and cardiometabolic profile in childhood: findings from a longitudinal birth cohort.* BJOG, 2015. **122**(12): p. 1664-73.
6. Abramowitz, A., E.S. Miller, and K.L. Wisner, *Treatment options for hyperemesis gravidarum.* Arch Womens Ment Health, 2017. **20**(3): p. 363-372.
7. Cole, L.A., *Biological functions of hCG and hCG-related molecules.* Reprod Biol Endocrinol, 2010. **8**: p. 102.
8. Festin, M., *Nausea and vomiting in early pregnancy.* BMJ Clin Evid, 2014. **2014**.
9. Grooten, I.J., T.J. Roseboom, and R.C. Painter, *Barriers and Challenges in Hyperemesis Gravidarum Research.* Nutr Metab Insights, 2015. **8**(Suppl 1): p. 33-9.
10. Grooten, I.J., et al., *Helicobacter pylori infection: a predictor of vomiting severity in pregnancy and adverse birth outcome.* Am J Obstet Gynecol, 2017. **216**(5): p. 512 e1-512 e9.
11. Davenport, M.H., et al., *Timing of excessive pregnancy-related weight gain and offspring adiposity at birth.* Obstet Gynecol, 2013. **122**(2 Pt 1): p. 255-61.
12. Hivert, M.F., et al., *Greater early and mid-pregnancy gestational weight gains are associated with excess adiposity in mid-childhood.* Obesity (Silver Spring), 2016. **24**(7): p. 1546-53.
13. Goldstein, R.F., et al., *Association of Gestational Weight Gain With Maternal and Infant Outcomes: A Systematic Review and Meta-analysis.* JAMA, 2017. **317**(21): p. 2207-2225.
14. Linne, Y., et al., *Long-term weight development in women: a 15-year follow-up of the effects of pregnancy.* Obes Res, 2004. **12**(7): p. 1166-78.
15. Loetscher, K.C., et al., *Ethnic-cultural background, maternal body size and pregnancy outcomes in a diverse Swiss cohort.* Women Health, 2007. **45**(2): p. 25-40.
16. IOM, *Weight Gain During Pregnancy: Reexamining the Guidelines*. 2009.
17. Josefson, J.L., et al., *Excessive gestational weight gain in the first trimester among women with normal glucose tolerance and resulting neonatal adiposity.* J Perinatol, 2016. **36**(12): p. 1034-1038.
18. Scott, C., et al., *No global consensus: a cross-sectional survey of maternal weight policies.* BMC Pregnancy Childbirth, 2014. **14**: p. 167.
19. Frischknecht, F., et al., *Changes in pre-pregnancy weight and weight gain during pregnancy: retrospective comparison between 1986 and 2004.* Swiss Med Wkly, 2009. **139**(3-4): p. 52-5.
20. G, P., *Influence of nutrition councelling and fitness courses on weight gain and mode of delivery in pregnacy*, in *Clinic of Obstetrics, Univesity Hospital Zurich*. 2017.
21. Lain, K.Y. and P.M. Catalano, *Metabolic changes in pregnancy.* Clin Obstet Gynecol, 2007. **50**(4): p. 938-48.
22. Blumfield, M.L., et al., *Systematic review and meta-analysis of energy and macronutrient intakes during pregnancy in developed countries.* Nutr Rev, 2012. **70**(6): p. 322-36.
23. Snophan, V.A. and K.C. Quack Loetscher, *Association of maternal macronutrient intake and the relative macroutrient distribution in maternal diet with urogenital infections during pregnancy*, in *Human Nutrition*. 2017, ETH.
24. Godfrey, K., et al., *Maternal nutrition in early and late pregnancy in relation to placental and fetal growth.* BMJ, 1996. **312**(7028): p. 410-4.
25. Ota, E., et al., *Antenatal dietary education and supplementation to increase energy and protein intake.* Cochrane Database Syst Rev, 2015(6): p. CD000032.
26. Olsen, S.F., et al., *Randomised clinical trials of fish oil supplementation in high risk pregnancies. Fish Oil Trials In Pregnancy (FOTIP) Team.* BJOG, 2000. **107**(3): p. 382-95.
27. Salvig, J.D. and R.F. Lamont, *Evidence regarding an effect of marine n-3 fatty acids on preterm birth: a systematic review and meta-analysis.* Acta Obstet Gynecol Scand, 2011. **90**(8): p. 825-38.

28. Perinatal Nutrition Working Group, a.p.o.t.N.H.M., Healthy Babies Coalition, *Benefits of Seafood Consumption and Omega-3 DHA During Pregnancy and Early Post-Natal Development*, in *White Paper*. 2012.
29. Parle-McDermott, A., et al., *Confirmation of the R653Q polymorphism of the trifunctional C1-synthase enzyme as a maternal risk for neural tube defects in the Irish population.* Eur J Hum Genet, 2006. **14**(6): p. 768-72.
30. Obeid, R., W. Holzgreve, and K. Pietrzik, *Is 5-methyltetrahydrofolate an alternative to folic acid for the prevention of neural tube defects?* J Perinat Med, 2013. **41**(5): p. 469-83.
31. Eichholzer, M., et al., *Folsäure ist unentbehrlich für die normale Entwicklung des Kindes*, B.f. Gesundheit, Editor. 2008: Bern.
32. Baerlocher, K., et al., *Folsäure: Expertenbericht der Eidgenössischen Ernährungskommission zur Prophylaxe von Neuralrohrdefekten*. 2002, Bundesamt für Gesundheit.
33. Viswanathan, M., et al., *Folic Acid Supplementation for the Prevention of Neural Tube Defects: An Updated Evidence Report and Systematic Review for the US Preventive Services Task Force.* JAMA, 2017. **317**(2): p. 190-203.
34. De-Regil, L.M., et al., *Effects and safety of periconceptional oral folate supplementation for preventing birth defects.* Cochrane Database Syst Rev, 2015(12): p. CD007950.
35. Stoffel, N.U., et al. *Maternal iron absorption and iron transfer to the fetus during pregnancy in normal-weight and overweight/obese women and the effects on infant iron status*. in *IUNS*. 2017. Buenos Aires.
36. Zhuang, T., H. Han, and Z. Yang, *Iron, oxidative stress and gestational diabetes.* Nutrients, 2014. **6**(9): p. 3968-80.
37. Zein, S., S. Rachidi, and I. Hininger-Favier, *Is oxidative stress induced by iron status associated with gestational diabetes mellitus?* J Trace Elem Med Biol, 2014. **28**(1): p. 65-9.
38. Chan, K.K., et al., *Iron supplement in pregnancy and development of gestational diabetes--a randomised placebo-controlled trial.* BJOG, 2009. **116**(6): p. 789-97; discussion 797-8.
39. Kinnunen, T.I., et al., *Supplemental iron intake and the risk of glucose intolerance in pregnancy: re-analysis of a randomised controlled trial in Finland.* Matern Child Nutr, 2016. **12**(1): p. 74-84.
40. Fu, S., et al., *The Relationship Between Body Iron Status, Iron Intake And Gestational Diabetes: A Systematic Review and Meta-Analysis.* Medicine (Baltimore), 2016. **95**(2): p. e2383.
41. Zhang, C. and S. Rawal, *Dietary iron intake, iron status, and gestational diabetes.* Am J Clin Nutr, 2017. **106**(Suppl 6): p. 1672S-1680S.
42. Breymann, C., Honegger, C., Holzgreve, W., Surbek, D., *Diagnostik und Therapie der Eisenmangelanämie in der Schwangerschaft und postnatal*, in *Expertenbrief No 22*. 2009.
43. Haider, B.A. and Z.A. Bhutta, *Multiple-micronutrient supplementation for women during pregnancy.* Cochrane Database Syst Rev, 2017. **4**: p. CD004905.
44. Richard, A., S. Rohrmann, and K.C. Quack Lotscher, *Prevalence of Vitamin D Deficiency and Its Associations with Skin Color in Pregnant Women in the First Trimester in a Sample from Switzerland.* Nutrients, 2017. **9**(3).
45. Keller, J.-P., et al., *Prevalence and determinants of vitamin D deficiency in the third trimester of pregnancy: a multicentric study in Switzerland.* British Journal of Nutrition, 2018.
46. DACH, *Referenzwerte für Nährstoffzufuhr*, Ö. DGE, SGE, Editor. 2012.
47. Ernährungskommission, E., *Vitamin D deficiency: Evidence, safety, and recommendations for the Swiss population*, E.r.o.t. FCN, Editor. 2012, Bundesamt für Gesundheit: Zürich.
48. Aghajafari, F., et al., *Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies.* BMJ, 2013. **346**: p. f1169.
49. Poel, Y.H., et al., *Vitamin D and gestational diabetes: a systematic review and meta-analysis.* Eur J Intern Med, 2012. **23**(5): p. 465-9.
50. Bodnar, L.M., et al., *Maternal vitamin D deficiency increases the risk of preeclampsia.* J Clin Endocrinol Metab, 2007. **92**(9): p. 3517-22.
51. Weinert, L.S., et al., *Serum vitamin D insufficiency is related to blood pressure in diabetic pregnancy.* Am J Hypertens, 2014. **27**(10): p. 1316-20.
52. Merewood, A., et al., *Association between vitamin D deficiency and primary cesarean section.* J Clin Endocrinol Metab, 2009. **94**(3): p. 940-5.
53. Scholl, T.O., X. Chen, and P. Stein, *Maternal vitamin D status and delivery by cesarean.* Nutrients, 2012. **4**(4): p. 319-30.

54. Qin, L.L., et al., *Does Maternal Vitamin D Deficiency Increase the Risk of Preterm Birth: A Meta-Analysis of Observational Studies.* Nutrients, 2016. **8**(5).
55. Bodnar, L.M. and H.N. Simhan, *Vitamin D may be a link to black-white disparities in adverse birth outcomes.* Obstet Gynecol Surv, 2010. **65**(4): p. 273-84.
56. Wagner, C.L., et al., *Health characteristics and outcomes of two randomized vitamin D supplementation trials during pregnancy: a combined analysis.* J Steroid Biochem Mol Biol, 2013. **136**: p. 313-20.
57. De-Regil, L.M., et al., *Vitamin D supplementation for women during pregnancy.* Cochrane Database Syst Rev, 2016(1): p. CD008873.
58. Agarwal, S., O. Kovilam, and D.K. Agrawal, *Vitamin D and its impact on maternal-fetal outcomes in pregnancy: A critical review.* Crit Rev Food Sci Nutr, 2016: p. 1-15.
59. Zhou, S.S., et al., *Vitamin D and risk of preterm birth: Up-to-date meta-analysis of randomized controlled trials and observational studies.* J Obstet Gynaecol Res, 2017. **43**(2): p. 247-256.
60. Ernährungskommission, E., *Iodine supply in Switzerland: Current Status and Recommendations*, in *Expert report of the FCN*. 2013, Bundesamt für Gesundheit: Zürich.
61. Andersson, M., et al., *The Swiss iodized salt program provides adequate iodine for school children and pregnant women, but weaning infants not receiving iodine-containing complementary foods as well as their mothers are iodine deficient.* J Clin Endocrinol Metab, 2010. **95**(12): p. 5217-24.
62. Zimmermann, M.B., et al., *Increasing the iodine concentration in the Swiss iodized salt program markedly improved iodine status in pregnant women and children: a 5-y prospective national study.* Am J Clin Nutr, 2005. **82**(2): p. 388-92.
63. Andersson, M., I. Herter-Aeberli, and M.B. Zimmermann, *The National Swiss Iodine Study 2015*. 2017.
64. Gowachirapant, S., et al., *Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial.* Lancet Diabetes Endocrinol, 2017. **5**(11): p. 853-863.
65. Koletzko, B., et al., *German national consensus recommendations on nutrition and lifestyle in pregnancy by the 'Healthy Start - Young Family Network'.* Ann Nutr Metab, 2013. **63**(4): p. 311-22.
66. SGE, Schweizerische Gesellschaft für Ernährung. *Schweizer Lebensmittelpyramide*. 2011 22.12.2017]; Available from: http://www.sge-ssn.ch/ich-und-du/essen-und-trinken/ausgewogen/schweizer-lebensmittelpyramide/.

8. Acknowledgements

Since the beginning of my career in research, many mentors, colleagues, co-workers and students from different countries have supported and guided my way to this Habilitationsschrift.

Firstly, I would like to express my sincere gratitude to Prof. Roland Zimmermann, Head of Obstetrics Department at the University Hospital Zurich, for his patience, motivation and continuous support over the past years. Without his broader view of the field of Obstetrics, I could not have done my work in this environment.
I had Prof. Renate Huch as a mentor at the beginning of my career. She encouraged me to find my "niche". She set the grounding stone for my research at the intersection of Obstetrics and Public Health. I am tremendously thankful to her for this help at the start. A special "thank you" goes to Dr. Andreas Zisch and PD Dr. Martin Ehrbar of the Research Unit of the Clinic of Obstetrics at the University Hospital Zurich. They gave me the opportunity to start my own research group.

I am particularly grateful to my research collaborators Prof. Sabine Rohrmann (EBPI Zurich), Dr. Nicole Schmidt (HUG Geneva), Dr. Maria Andersson and Dr. Isabelle Herter (Human Nutrition Department, ETH) for their scientific support and the many hours of intensive discussions to find a way to improve the lives and lifestyles of pregnant women.
I would like to deeply thank Prof. Barbara Abrams and Prof. Steve Selvin from the University of California, Berkeley, USA, as my special collaborators and mentors for teaching me to see the problems and the chances in the field of nutrition in Obstetrics.

I would also like to sincerely thank Sibylle Abt (Head of Verein PEBS) for her long support in the implementation and development of nutrition counselling and fitness classes for pregnant women and mothers to improve the lives for all their babies. Transforming research into action should be the goal of every public health research.

Many thanks to co-workers Dr. Aline Richard, Dr. Jean-Philippe Keller, Dr. Sophie Cabaset, MD students Dr. Martina Fässler, Dr. Cornelia Estermann, Dr. Kerstin

Blickenstorfer and master's students (ETH) Viola Snophan and Giulia Pestoni. It was, and still is, extremely stimulating to work with them.

Finally, special thanks go to all unnamed colleagues, friends, and relatives who supported my scientific career.

This thesis is gratefully dedicated to Christina and Hans Quack, my parents, who laid the ground for all my work, and my family Sven, Vincent, Eric and Maurice. Thank you for letting me do my work.